

Genetic Influences in Irritable Bowel Syndrome: A Twin Study

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BACKGROUND: Aggregation of symptoms of abdominal pain or bowel disturbance has been described in the families of patients with irritable bowel syndrome (IBS). This may be due to environmental factors, including learned responses to abdominal symptoms or a genetic contribution to the etiology of IBS.

OBJECTIVES: To determine the relative contribution of genetic factors to IBS by evaluating IBS symptoms in monozygotic (MZ) and dizygotic (DZ) twins.

METHODS: A total of 4,480 unselected twin pairs identified from a national volunteer twin register were asked to complete a validated questionnaire. IBS was defined by the Rome II criteria.

RESULTS: A total of 5,032 subjects replied (56% response rate). One thousand eight hundred seventy complete twin pairs were evaluable; 888 MZ pairs (82 male pairs, mean age 51, SD 13 (range 19–81) yr) and 982 DZ pairs (69 male pairs, age 52, SD 13 (20–82) yr). The prevalence of IBS was 17% in MZ and 16% in DZ twins. There was no significant difference in casewise concordance rates between the MZ and DZ twins (28% vs 27%, $p = \text{NS}$). Logistic regression analysis revealed that decreasing age and increasing psychosomatic score were independently associated with IBS. Multifactorial liability threshold modeling suggested that a combination of unique and shared environmental factors provided the best model for IBS. In contrast, somatization was shown to be moderately heritable.

CONCLUSION: Genetic factors are of little or no influence on IBS where the predominant influences appear to be environmental.

(Am J Gastroenterol 2005;100:1340–1344)

INTRODUCTION

In community surveys, 10–22% of adults in the United Kingdom report symptoms consistent with irritable bowel syndrome (IBS) (1, 2). IBS significantly impairs patients' quality of life, with over 40% of patients reporting avoiding everyday activities such as eating certain foods, sex, socializing, traveling, and exercise (3). Furthermore, although the direct annual costs in the United Kingdom attributable to IBS have been conservatively estimated to be £22 million (4), indirect costs are likely to be substantial, due to the doubling of workdays lost in subjects with IBS compared with the normal population (5).

A number of studies have examined the role of familial factors in the etiology of IBS. Aggregation of abdominal symptoms and IBS in families of patients with IBS has been described (6, 7). However, this may be due to genetic factors or to shared exposure to environmental factors, including learned responses to visceral stimuli. Two previous studies of functional bowel symptoms in twins have suggested that genetic factors contribute to the etiology of IBS (8, 9). How-

ever, in one of these studies a parental history of IBS was a stronger predictor of IBS than having a twin with IBS, suggesting social learning was more important than genetic factors in the etiology of this disorder (9).

We have evaluated the contribution of genetic factors to IBS by comparing concordance rates for IBS defined by the Rome II criteria (10) in pairs of monozygotic (MZ) and dizygotic (DZ) twins.

METHODS

Subjects

All 4,480 pairs of twins from the St Thomas' Adult UK Twin Registry (TwinsUK) (11) were invited to take part in the study. All are healthy volunteers who were recruited through a national media campaign and from twin registers (12). The zygosity of the twins was established using a standardized questionnaire with genotyping in cases of uncertainty (13).

The study was approved by the St. Thomas' Hospital Research Ethics Committee and the twin volunteers gave

informed consent, but were unaware of the precise question being addressed by the study.

Questionnaire

Questions relating to demographic details, symptoms of IBS during the past year, potential risk factors for IBS (alcohol intake, body mass index (BMI), drug therapy, handedness, and smoking), and a psychosomatic symptom checklist were included in a questionnaire sent to the twins. The questionnaire covered a number of topics and the twins were unaware of the hypothesis of our study. The psychosomatic checklist consisted of 16 complaints recorded on a scale of 0–4 concerning both their frequency and severity. A final score was obtained by summing the products of the frequency and severity of each item (14).

The IBS questions have been validated in 100 community subjects and have good validity for a diagnosis of IBS (based on the Rome II criteria) against an interview ($\kappa = 0.76$) and very good reliability on retest 4 wk later in the 60 subjects who responded to a second postal questionnaire ($\kappa = 0.85$). The questions also had good validity against a diagnosis of IBS by a consultant physician, who was blinded to the results of the questionnaire, in 125 unselected patients attending a gastroenterology outpatient department ($\kappa = 0.61$).

Twin Studies

An individual's phenotype is the result of the effects of both genotype and environment. To study the source of individual differences (*i.e.*, the variance) in a phenotype, genetically related subjects are required and twins are just such a group. MZ twins share the same genetic makeup and DZ twins share on average 50% of their segregating genes. It is assumed that both types of twins have been exposed to the same family or shared environment (15) and, therefore, any greater similarity between MZ than DZ twins is due to genetic influences.

Analysis

A subject was considered to have IBS if it fulfilled the Rome II criteria of abdominal pain for at least 12 wk in the last year with two of: relief with defecation; change in stool frequency with pain; change in stool consistency with pain (10).

Concordance is a measure of the proportion of co-twins of affected twins that have the disorder themselves. Casewise concordance is the probability that a twin is affected given that the co-twin is affected. It is calculated from the formula $2c/(2c + d)$, where c is the number of concordant pairs and d the number of discordant pairs (16).

Genetic Modeling

Quantitative genetic model fitting is based on comparison of the covariance (or correlation) of the disorder between MZ and DZ twins (17, 18). It allows separation of the observed phenotypic variance into additive genetic components A (multiple small genetic effects) and environmental components shared by both twins (C) and unique to each twin (E).

The maximum likelihood modeling method used in twin study analysis assumes that variation in the underlying li-

ability of the disorder is normally distributed (17). For dichotomous traits, the correlation in liability among twins can be estimated from the frequencies of IBS concordant and IBS discordant pairs using a multifactorial liability threshold model (17, 19, 20). Thus, the significance of the variance components A and C is assessed by removing each in submodels and testing the deterioration in fit compared with the full model. The purpose of the model-fitting procedure is to explain the pattern of observed variances and covariances using as few parameters (A , C , and E) as possible.

Statistical Analysis

Demographic differences between the MZ and DZ twins were compared using generalized estimating equations, which correct for relatedness of the twins in a pair. The difference in concordance rates for IBS between MZ and DZ twins was compared using the χ^2 test. Multivariate stepwise forward logistic regression analysis was used to assess the independent contribution of variables (age, alcohol, BMI, drug therapy, gender, handedness, psychosomatic score, and smoking) to IBS, including twin status as a confounder since the twins are not independent of each other. In the genetic modeling, submodels were compared with the full model by hierarchic χ^2 tests and the significance of the change in χ^2 goodness-of-fit statistic was assessed. Data handling and preliminary analyses were performed using STATA (21). Genetic modeling of both IBS and the continuous data for psychosomatic score, based on the variance–covariance matrices of MZ and DZ twins, was performed using the statistical program Mx (22).

RESULTS

A total of 5,032 subjects returned a completed questionnaire (56% response rate). One thousand eight hundred seventy complete twin pairs were evaluable comprising 888 MZ pairs and 982 same gender DZ pairs. The demographic details of the two groups are shown in Table 1. The two groups were well matched for age, drug therapy, excess alcohol, psychosomatic score, and handedness, but DZ twins had a slightly but significantly higher BMI and were slightly more likely to have ever smoked.

The concordance rates for IBS in the MZ and DZ twins are shown in Table 2. There was no significant difference in the casewise concordance (MZ 28% vs DZ 27%, $p = \text{NS}$) rates for IBS. Limiting the analysis of concordance to twins with a narrower category of frequent IBS symptoms at least once a week (MZ 17% vs DZ 18%, $p = \text{NS}$), or more than once a week (MZ 16% vs DZ 14%, $p = \text{NS}$) also revealed no significant difference between MZ and DZ twins. Furthermore, confining the analysis to twins under the age of 40 revealed no difference in concordance (MZ 32% vs DZ 37%, $p = \text{NS}$).

The results of univariate logistic regression analysis for risk factors for IBS expressed as odds ratios are shown in Table 3. Female gender, psychosomatic score, anticholinergic

Table 1. The Demographic Details of the Twins Studied

	Monozygotic Twins (n = 1,776)	Dizygotic Twins (n = 1,964)	p-Value
Age (yr)	51 (19–81)*	52 (20–82)*	0.19
Female	91%	93%	0.08
Prevalence IBS	17%	16%	0.27
Body mass index (kg/m ²)	24.9 (14–47)*	25.3 (15–54)*	0.04
Ever smoked	36%	46%	<0.01
Excess alcohol **	4%	5%	0.27
Anticholinergic drug therapy	7%	6%	0.24
Oral contraceptive or hormone replacement therapy	24%	26%	0.18
Psychosomatic score	13 (0–145)***	14 (0–199)***	0.21
Right handed	89%	88%	0.78

p-Values are corrected for relatedness of the twins.

* Mean (range).

** Excess alcohol intake was defined as >28 units per week for a man and >21 units per week for a woman.

*** Median (range).

drug therapy, excess alcohol, and hormone replacement therapy/oral contraceptive medication use were associated with IBS. Increasing age was negatively associated with IBS. BMI, smoking, and handedness were not associated with IBS. Multivariate logistic regression analysis revealed that only age (odds ratio 0.98 (95% CI 0.97–0.98), $p < 0.001$) and psychosomatic score (odds ratio 1.02 (95% CI 1.02–1.03), $p < 0.001$) were independently associated with IBS.

The results of the genetic modeling analysis for IBS are shown in Table 4. Model fitting revealed that additive genetic effects (A) could be dropped from the model without significantly worsening the χ^2 goodness-of-fit statistic. However, the effects of the shared environment of the twins (C) could not be eliminated. A model containing parameters for only the shared environment (C) and the unique environment of the twins (E) best explained the variance in liability to IBS within this population. Twenty-six percent of the variance in liability to IBS was due to the shared environment and 74% due to the unique environment of the twins.

Since the psychosomatic score data were skewed and deviated significantly from a normal distribution, the data were log transformed to create a new variable $\ln(\pm \exp(-k))$. The value and sign of k were chosen so that the skewness of the new psychosomatic score variable would be 0. The results of the genetic modeling analysis for psychosomatic score are shown in Table 5. Model fitting revealed that neither additive genetic (A) nor shared environmental factors (C) could be dropped without significantly affecting the fit of the model. The ACE model, therefore, provided the best fit and explanation for the variance in psychosomatic score within this population. Heritability for psychosomatic score was estimated to be 39% (95% CI 23–54%).

DISCUSSION

Irritable bowel syndrome is a group of functional bowel disorders in which abdominal discomfort or pain is associated with defecation or alteration of stool frequency or form, in the absence of known pathology of structure (23). A number of factors have been implicated in the etiology of IBS including visceral hypersensitivity, psychological morbidity,

abnormal illness behavior, the influence of mood on gut function, postinfective bowel dysfunction, and diet (23). Both environmental and genetic familial influences may potentially contribute to a number of these etiological factors.

Two studies have examined the influence of familial factors in IBS. Reporting a first-degree relative with abdominal pain or bowel problems was associated with IBS in a community study (6). A subsequent study contacted first-degree relatives of patients with IBS and the relatives of their spouses and found that IBS by the Manning or Rome I criteria was over twice as common among the relatives of the patients (7).

Familial aggregation studies do not distinguish between genetic and shared environmental factors. Twin studies permit the relative contribution of environmental and genetic factors to be determined by examining the concordance rates in MZ and DZ twins. In an Australian study, a group of twins were asked whether they had “ever had a lot of trouble” with five common abdominal symptoms and if a doctor had diagnosed a functional bowel disorder (8). Although concordance rates for functional bowel disorder were very low, they were higher among MZ twins, suggesting a genetic contribution. In a subsequent larger study, higher concordance rates for reporting a twin with IBS were again found in MZ twins (9). However, in this study a parental family history of IBS was found to be a more significant predictor of IBS than having a twin with IBS, suggesting that parent–child interactions were more important than genetic influences in IBS (9).

In the present study, there was no significant difference in the concordance rates for IBS defined by the Rome II criteria in MZ and DZ twins. Genetic modeling suggested that variance in the liability to IBS in the population studied was

Table 2. Concordance Rates for Irritable Bowel Syndrome in the Monozygotic and Dizygotic twins

Twin Type	Total Pairs	Discordant Pairs	Concordant Affected Pairs	Casewise Concordance Rate*
Monozygotic	888	220	42	28 (21–34)%
Dizygotic	982	224	42	27 (21–34)%

* 95% confidence intervals in parentheses.

Table 3. Univariate Logistic Regression Analysis of Potential Risk Factors for Irritable Bowel Syndrome in the Study Population

Variable	IBS	No IBS	Odds Ratio (95% CI)	p-Value
Age	49.6 (21–79)*	52.3 (19–82)*	0.98 (0.98–0.99)	<0.001
Anticholinergic drug therapy	8.7%	5.8%	1.54 (1.12–2.12)	0.008
Body mass index	25.3 (16–47)*	25.0 (14–54)*	1.02 (0.99–1.04)	0.13
Ever smoked	42.6%	40.7%	1.08 (0.91–1.29)	0.39
Excess alcohol**	6.4%	4.3%	1.52 (1.04–2.21)	0.03
Female	94.8%	91.4%	1.71 (1.17–2.50)	0.005
Oral contraceptive or hormone replacement therapy	29.3%	24.5%	1.27 (1.05–1.54)	0.01
Psychosomatic score	26 (0–199)***	12 (0–153)***	1.02 (1.02–1.03)	<0.001
Right handed	88.6%	88.5%	0.99 (0.76–1.31)	0.96

* Mean (range).

** Excess alcohol intake was defined as >28 units per week for a man and >21 units per week for a woman.

*** Median (range).

explained best by shared and unique environmental factors. A genetic influence on the liability to IBS in the population studied cannot be entirely excluded but environmental factors appear to be far more important. Younger age and increasing psychosomatic score were independently associated with IBS. However, unique environmental factors accounted for 75% of the variance in IBS in the study population and further work is required to define environmental risk factors for IBS.

Why are the results of the present study apparently different from the two previous twin studies of IBS? Firstly, different criteria were used to define the study populations. A medical diagnosis of “functional abdominal symptoms” (8) and a self-reported diagnosis of “irritable bowel syndrome” (9) were used in the previous studies, whereas we have utilized the symptom-based Rome II criteria. Secondly, the prevalence of IBS in the present study (17%) was much higher than the previous twin studies (3% and 5%) (8, 9), though our figures are comparable to community studies of IBS in the United Kingdom (1, 2). Thirdly, the frequency of symptoms may have been different. However, confining the analysis in the present study to twins with frequent symptoms of IBS revealed the same results, suggesting that the differences do not relate to symptom frequency. Fourthly, the demographics of the twin populations studied also differ. The two previous studies examined groups of twins who were on average 15–20 yr younger, with higher numbers of males compared with the present study (8, 9). Male gender and increasing age have been reported to be negatively associated with IBS (23), and these associations were confirmed in the current study. It is conceivable that genetic factors have a more important role in the etiology of IBS in younger and male subjects. However, confining the analysis of IBS in the present study to

twins under the age of 40 revealed no difference in concordance making this explanation unlikely. Finally, differences in selection and in particular somatization between the study populations may have contributed. In a familial aggregation study, it was noted that somatization explained most of the familial clustering found (7). The authors suggested that familial aggregation of IBS might be due to familial somatization (7). Genetic factors were reported to account for at least half of the variance in somatization in a large twin study (24) and genetic modeling in the present study revealed a significant genetic contribution to psychosomatic score among the twins. Somatization is common among IBS patients in a hospital setting (25). It is, therefore, likely that the prevalence of somatization was much higher in the subjects with IBS in the two previous twin studies, since both studies depended on a clinical diagnosis of IBS, and that there appeared to be a significant genetic contribution to IBS in these studies due to confounding due to somatization.

For the vast majority of traits and conditions twins are generalizable to singletons. Moreover, the prevalence of a number of common medical conditions and lifestyle characteristics among twins from the St Thomas' Adult UK Twin Registry has been found to be very similar to a population drawn from general practice (26). However, our study cannot be directly generalized to males, as the twin population examined was largely female. The twin registry has a female bias for historical reasons.

In conclusion, although we found somatization to be moderately heritable, we found no significant difference in concordance rates for IBS defined by the Rome II criteria in MZ and DZ twins. Although a minor genetic contribution cannot be excluded, environmental factors appear to predominate in the etiology of IBS.

Table 4. Genetic Modeling Analysis for Irritable Bowel Syndrome

Model	A (95% CI)	C (95% CI)	E (95% CI)	Difference in χ^2	p-Value for difference in χ^2
ACE	0 (0–0.32)	0.26 (0–0.35)	0.74 (0.62–0.83)	–	–
AE	0.31 (0.19–0.42)	–	0.69 (0.58–0.81)	3.96	<0.05*
CE	–	0.26 (0.17–0.35)	0.74 (0.65–0.83)	0	>0.99*

A, additive genetic; C, common environment; E, unique environment.

*Compared with ACE model.

Best fitting model in bold—fewest components without causing significant deterioration in χ^2 goodness-of-fit statistic.

Table 5. Genetic Modeling Analysis for Psychosomatic Score

Model	A (95% CI)	C (95% CI)	E (95% CI)	Difference in χ^2	<i>p</i> -Value for Difference in χ^2
ACE	0.39 (0.23–0.54)	0.16 (0.02–0.28)	0.45 (0.41–0.50)	–	–
AE	0.56 (0.52–0.60)	–	0.44 (0.40–0.48)	5.1	0.02*
CE	–	0.45 (0.41–0.48)	0.55 (0.52–0.59)	25.3	<0.001*

A, additive genetic; C; common environment; E; unique environment.

*Compared with ACE model.

Best fitting model in bold—other models cause significant deterioration in χ^2 goodness-of-fit statistic.

ACKNOWLEDGMENTS

We are grateful to Bridget Gunson (Liver Laboratories, University Hospital, Birmingham) for initial data processing and analysis. We gratefully acknowledge financial support from Janssen Pharmaceuticals, Knoll, and Wyeth Laboratories. The Twin Research & Genetic Epidemiology Unit receives financial support from the Arthritis Research Campaign, British Heart Foundation, Chronic Disease Research Foundation, the European Commission 5th framework program (no. QLG2-CT-2002-01254) GenomEUtwin grant, and a DNA Resource grant from the Wellcome Trust.

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Received October 21, 2004; accepted December 9, 2004.

REFERENCES

- Heaton KW, O'Donnell LJD, Braddon FEM, et al. Symptoms of irritable bowel syndrome in a British urban community: Consulters and nonconsulters. *Gastroenterology* 1992;102:1962–7.
- Jones R, Lydeard S. Irritable bowel syndrome in the general population. *BMJ* 1992;304:87–90.
- Corney RH, Stanton R. Physical symptom severity, psychological and social dysfunction in a series of outpatients with irritable bowel syndrome. *J Psychosom Res* 1990;34:483–91.
- Wells NEJ, Hahn BA, Whorwell PJ. Clinical economics review: Irritable bowel syndrome. *Aliment Pharmacol Ther* 1997;11:1019–30.
- Drossman DA, Li Z, Andruzzi E, et al. Householder survey of functional gastrointestinal disorders: Prevalence, sociodemography and health impact. *Dig Dis Sci* 1993;38:1569–80.
- Locke GR, Zinsmeister AR, Talley NJ, et al. Familial association in adults with functional gastrointestinal disorders. *Mayo Clin Proc* 2000;75:907–12.
- Kalantar JS, Locke GR, Zinsmeister AR, et al. Familial aggregation of irritable bowel syndrome: A prospective study. *Gut* 2003;52:1703–7.
- Morris-Yates A, Talley NJ, Boyce PM, et al. Evidence of genetic contribution to functional bowel disorder. *Am J Gastroenterol* 1998;93:1311–7.
- Levy RL, Jones RK, Whitehead WE, et al. Irritable bowel syndrome in twins: Heredity and social learning both contribute to etiology. *Gastroenterology* 2001;121:799–804.
- Thompson WG, Longstreth GF, Drossman DA, et al. Functional bowel disorders and functional abdominal pain. *Gut* 1999;45(suppl II):43–7.
- Spector TD, MacGregor AJ. The St Thomas' Adult UK Twin Registry. *Twin Res* 2002;5:440–3.
- Spector TD, Cicuttini F, Baker J, et al. Genetic influences on osteoarthritis in women: A twin study. *BMJ* 1996;312:940–4.
- Martin NG, Martin PG. The inheritance of scholastic abilities in a sample of twins. Ascertainments of the sample and diagnosis of zygosity. *Ann Hum Genet* 1975;39:213–8.
- Attanasio V, Andrasik F, Blanchard EB, et al. Psychometric properties of the SUNYA revision of the psychosomatic symptom checklist. *J Behav Med* 1984;7:247–57.
- Kyvik KO. Generalisability and assumptions of twin studies. In: Spector TD, Sneider H, Macgregor AJ, eds. *Advances in twin and sib-pair analysis*. London: Greenwich Medical Media, 2000.
- Macgregor AJ. Practical approaches to account for bias and confounding in twin data. In: Spector TD, Sneider H, Macgregor AJ, eds. *Advances in twin and sib-pair analysis*. London: Greenwich Medical Media, 2000.
- Neale MC, Cardon LR. *Methodology for genetic studies of twins and families*. Dordrecht: Kluwer Academic Publishers, 1992.
- Sneider H, Boomsma DI, Van Doornen LJP. Heritability of respiratory sinus arrhythmia: Dependency on task and respiration rate. *Psychophysiology* 1997;34:317–28.
- Falconer DS. *Introduction to quantitative genetics*. Harlow: Longman Scientific and Technical, 1989.
- Sham PC, Walters EE, Neale MC, et al. Logistic regression analysis of twin data: Estimation of parameters of the multifactorial liability-threshold model. *Behaviour Genetics* 1994;24:229–38.
- Intercooled Stata for Windows 95. (version 5.0). College Station, Texas, USA: Statacorp, 1997.
- Neale MC. *Mx: statistical modelling* (4th edn.). Richmond, VA: Department of Psychiatry, Medical College of Virginia, 1997.
- Jones J, Boorman J, Cann P, et al. British Society of Gastroenterology guidelines for the management of the irritable bowel syndrome. *Gut* 2000;47(suppl II):1–19.
- Kendler KS, Walters EE, Truett KR, et al. A twin-family study of self-report symptoms of panic-phobia and somatization. *Behav Genet* 1995;25:499–515.
- Miller AR, North CS, Clouse RE, et al. The association of irritable bowel syndrome and somatization disorder. *Ann Clin Psychiatry* 2001;13:25–30.
- Andrew T, Hart DJ, Sneider H, et al. Are twins and singletons comparable? A study of disease-related and lifestyle characteristics in adult women. *Twin Research* 2001;4:464–77.