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Appendectomy in Australian Twins

To the Editor:

We read with great interest the recent article by Basta et al. (1990) on the genetics of acute appendicitis. Family studies such as this can overestimate heritability if family environment is a significant covariate of disease, unless some measure of this is included in the analysis. We felt it might be useful to present appendectomy data from the Australian NH&MRC Twin Registry (ATR), as the classical twin study allows one to estimate the effects of shared environment.

In 1980, all 5,967 pairs of twins over the age of 18 years registered with the ATR (a population-based volunteer registry) were surveyed by mailed questionnaire for a past history of a number of diseases and operations. A total of 3,808 complete pairs returned the questionnaire, a 65% pairwise response rate. In one item, twins were asked to indicate whether they had previously undergone appendectomy and at what age the procedure was performed. Zygosity of twins was determined by response to two questionnaire items (Kasriel and Eaves 1976) and, in ambiguous cases, by the examination of photographs sent in by the twins.

Approximately 21% of all respondents had undergone appendectomy (see table 1), excluding 96 cases where the procedure was performed in the same year as a cholecystectomy or hysterectomy (procedures during which a prophylactic appendectomy is often performed). Females were more likely to report appendectomy than were males, a finding noted in other studies (Phlanz 1978). Mean age at time of operation was 19.5 years for females and 20.0 years for males (difference not significant). The rate of reported childhood appendectomy (i.e., before 18 years of age) increased monotonically from 9% of those born 1955–68 to 15% of those born 1925–34, falling off in earlier-born cohorts.

Overall, MZ female twin pairs were significantly more concordant than were DZ female twins, but MZ and DZ same-sex male pairs showed no such difference in concordance (see table 2). We then performed path analysis under the assumptions of the multifactorial threshold model (as applied to twins) implemented using the weighted least squares (WLS) option in LISREL 7.16 (Heath et al. 1989; Joreskog and Sorbom 1989). The path models tested contained an additive genetic component (G), a shared environmental component (C), a unique environmental component (E), and the age of the twins. There was no significant evidence for heterogeneity of causes in the sexes (homogeneity χ^2_3 = 0.05, P = .99), and a model comprising an additive genetic and shared environmental components fitted the data well (see table 3). Similar results were derived on stratifying the subjects into three age cohorts (data not shown).

There was also a suggestion of higher concordance

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Table 1

Age-specific Cumulative Rates of Appendectomy

	Age Range (years)					
	18–25	26–35	36–45	46–55	56–65	65+
Females:						
Rate	11.6%	22.9%	34.2%	35.6%	35.6%	30.1%
Sample size	1,522	1,484	783	534	353	193
Males:						
Rate	10.1%	17.0%	25.6%	27.1%	25.2%	20.4%
Sample size	1,032	830	367	258	143	113

Table 2

Twin Concordances and Tetrachoric Correlations

Twin Group	Total No. of Pairs	No. of + +[a]	No. of + −[a]	No. of − −[a]	r	SE
MZ:						
Female pairs	1,232	150	312	770	.52	.04
Male pairs	567	36	130	401	.40	.08
DZ:						
Female pairs	751	70	217	464	.35	.06
Male pairs	352	19	68	265	.45	.10
Female/male pairs	906	58	233	615	.32	.06

[a] + = Twin underwent appendectomy; − = twin did not undergo appendectomy.

Table 3

Tests of Genetic Hypotheses for Appendectomy, Fitted to Five Twin Groups

Model Number (type)	Proportion of Variance of Liability Due to				LR χ^2 Test of Fit		
	G	C	E	Age	χ^2	df	P
1 (GCE)	.27	.16	.51	.06	10.02	12	.62
2 (GE)	.46	...	.48	.06	13.35	13	.42
3 (CE)	...	.37	.57	.06	16.00	13	.25
4 (GCE):							
Males	.01	.35	.58	.06			
Females	.33	.13	.48	.06	6.79	8	.56

Note.—Hierarchic testing: model 2 vs. model 1, $\chi^2 = 3.33$, $P = .07$; model 3 vs. model 1, $\chi^2 = 5.98$, $P = .01$ (model 4 is the alternative sex-limitation model).

for age at appendectomy in MZ twins than in DZ twins; for pairs concordant for appendectomy performed prior to age 18 years, $r_{MZ} = .52$ (73 pairs, $P = .001$) and $r_{DZ} = .29$ (65 pairs, $P = .02$; intracorrelation difference $z = 1.8$, $P_{1-tail} = .03$). A formal evaluation of genetic architecture involved here would require use of the methods of Neale et al. (1989).

In conclusion, we present further evidence for the role of heredity in appendicitis and estimate the heritability of this condition to be approximately 27% (95% confidence interval 10%–50%), and the domesticity or cultural transmissibility to be 16% (range 3%–40%). These findings are in broad agreement with those of Basta et al.

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A Likelihood-based Analysis of Consistent Linkage of a Disease Locus to Two Nonsyntenic Marker Loci: Osteogenesis Imperfecta versus COL1A1 and COL1A2

To the Editor:

Sykes et al. (1990) have collected an impressive set of pedigrees segregating for a dominant form of osteogenesis imperfecta (OI), in order to address the question of whether all such families are linked to at least one of two nonsyntenic collagen loci. They employ the following approximation for the probability (P_i) that a given pedigree i is consistent with linkage at $\theta = .0$ to either one of the collagen loci: $P_i = \alpha + (1 - \alpha)(2/L_i^{\max})$, where α is the population frequency of families linked to either collagen locus and where $L_i^{\max}$ is the higher of the two pairwise likelihood ratios in favor of linkage at $\theta = .0$. Unfortunately, their approximation is unsatisfactory, since, if $0 \leqslant \alpha < 1$, then the probability P_i will be >1.0 whenever $L_i^{\max} < 2$ or the lod score is $< \log_{10}(2.0) \approx 0.3010$. In fact, if the lod score of 0.3 that they report for family 3.5 is actually <0.3010, then $P_{3.5} > 1.0$ for all values of $\alpha < 1$. Also, it is not clear how the data on family 6.3 could be used in their approximation: Since family 6.3 has a lod score of $-\infty$ with COL1A1 and a lod score of 0.0 (noninformative) with COL1A2, then $L_{6.3}^{\max}$ is 1.0, which implies that the "probability" $P_{6.3}$ is $(2 - \alpha) \geqslant 1.0$. How can a probability be >1?

Rather than rely on approximations, I suggest a likelihood-based approach: Let the two *nonsyntenic* collagen loci be referred to as marker 1 and marker 2. Let the event A = {the disease is linked to marker 1 at $\theta = .0$} and let B = {the disease is linked to marker 2 at $\theta = .0$}. Since markers 1 and 2 are candidate loci, the complementary event A^c is {the disease is unlinked to marker 1}; likewise, B^c is {the disease is unlinked to marker 2}. Let X represent the pedigree data, which consist of the disease data D, the marker 1 data $M1$, and the marker 2 data $M2$, so $X = (D, M1, M2)$. Let

$$\begin{aligned}\alpha_{A,B^c} &= P(A \text{ and not } B)\\ \alpha_{A^c,B} &= P(\text{not } A \text{ and } B)\\ \alpha_{A^c,B^c} &= P(\text{not } A \text{ and not } B)\\ \alpha_{A,B} &= P(A \text{ and } B),\end{aligned}$$

where the α's must sum to one. Then we would like to find the support interval for α_{A^c,B^c}, i.e., the proportion of pedigrees unlinked to both marker 1 and marker 2. This requires calculation of the probability (or likelihood) of the data X as a function of the alphas:

$$P(X) = P(X|A,B^c)\alpha_{A,B^c} + P(X|A^c,B)\alpha_{A^c,B} + P(X|A,B)\alpha_{A,B} + P(X|A^c,B^c)\alpha_{A^c,B^c}.$$

Note that $P(X|A,B^c) = P(D,M1|A,B^c)P(M2|A,B^c) = P(D,M1|A)P(M2)$, where $P(D,M1|A)$ can be calculated from the pairwise lod score between the disease and marker 1 and where $P(M2)$ is the probability of the observed marker 2 phenotypes on the pedigree. To employ similar reasoning,

$$\begin{aligned}P(X) = {} & P(D,M1|A)P(M2)\alpha_{A,B^c} + P(M1)P(D,M2|B)\alpha_{A^c,B} + P(X|A,B)\alpha_{A,B} + \\ & P(D)P(M1)P(M2)(1 - \alpha_{A^c,B} - \alpha_{A,B^c} - \alpha_{A,B}). \quad (1)\end{aligned}$$

The probability $P(X|A,B)$ in equation (1) cannot be calculated without assuming a two-locus model. This problem may be avoided by making the realistic assumption that $\alpha_{A,B} = 0$, i.e., the disease is never linked to *both* marker 1 and marker 2 simultaneously, which results in