

# The Influence of Genetics and Environmental Factors in the Pathogenesis of Acne: A Twin Study of Acne in Women

V. Bataille,\*† H. Snieder,\* A. J. MacGregor,\*‡ P. Sasieni,‡ and T. D. Spector\*

\*Twin Research and Genetic Epidemiology Unit, St Thomas' Hospital, London, U.K.; †Georgia Prevention Institute, Medical College of Georgia, Augusta, GA, U.S.A.; ‡Department of Mathematics, Statistics and Epidemiology, Cancer Research U.K., London, U.K.

Acne is common and often leads to significant psychological and physical morbidity. From clinical experience, acne appears to run in families; however, very few studies have investigated the genetic basis of this very common skin disease. A large twin study based on 458 pairs of monozygotic and 1099 pairs of dizygotic twins, all women with a mean age of 46 y was performed to investigate the relative contribution of genetic and environmental factors on the liability to acne. In addition, potential risk factors were assessed in twins with and without acne in a nested cross-sectional design. Fourteen percent of the twins reported a history of acne. Genetic modeling using acne scores showed that 81% (95% confidence interval 73–87%) of the variance of the disease was attributable to additive genetic effects. The remaining 19% was attributed to unique (i.e., unshared) environmental factors. Of the potential risk factors

tested in 400 acne twins and 2414 unaffected twins, only apolipoprotein A1 serum levels were significantly lower in acne twins even after adjusting for age and weight. Family history of acne was also significantly associated with an increased risk. No significant differences were found between acne twins and nonacne twins for weight, body mass index, height, birth weight, hair thinning, reproductive factors as well as cholesterol, triglycerides, high-density lipoprotein, and glucose levels. The lower serum levels of apolipoprotein A1 in acne twins were also confirmed when analyzing acne discordant twin pairs. The evidence of a major genetic influence on acne should stimulate the search for potential genes that may lead to new therapeutic approaches. **Key words:** acne/case-control study/genetics/twin study. *J Invest Dermatol* 119:1317–1322, 2002

Acne is one of the commonest skin diseases affecting between 40 and 50 million individuals in the U.S.A. alone with peak incidence in adolescence and mid-thirties in women (White, 1998). The expenditure for acne-prescribed drugs has been estimated at \$4 billion worldwide. In 1992, in the U.K. alone there were about 3.5 million consultations for acne in the primary care sector (Simpson, 1994). The facial disfigurement caused by moderate to severe acne is important socially and economically as acne can cause difficulties in finding employment, low self-esteem, and depression (Cunliffe, 1986; Motley and Finlay, 1992; Gupta and Gupta, 1998). Despite the prevailing lay view that acne is caused by environmental factors, a U.K. study reported that cosmetics, prescribed drugs, and occupation were not associated with acne (Goulden *et al*, 1999a).

The pathogenesis of acne has not yet been elucidated but scant data from family studies suggest familial clustering (Goulden *et al*, 1999a,b). A few twin studies have previously been published investigating the genetics of acne. One study by Friedman reported high heritability estimates for acne in twins recruited from a large U.S. twin registry (Friedman, 1984). The diagnosis of acne was assessed from nonstandardized medical records retrieved from each twin within a pair but twins were not interviewed for the study. A preliminary report of a recent twin

study of acne also showed high heritability estimates for acne in adolescent twins recruited from an Australian twin registry (Kirk *et al*, 2001). A twin study investigating sebum excretion in 40 pairs of adolescent acne twins found higher correlations in monozygotic *vs* dizygotic twins, but the numbers were small (Walton *et al*, 1988). The proportion of branched fatty acids in the sebaceous wax esters has also been reported to be more highly correlated in monozygotic twins compared with dizygotic twins (Stewart *et al*, 1986).

The combined twin and nested cross-sectional study reported here was set up to investigate potential environmental, hormonal, and metabolic as well as genetic risk factors for this disease, and also to quantify the relative contribution of genetic and environmental factors in acne causation using a large population-based sample of Caucasian female monozygotic and dizygotic twin pairs recruited from all over the U.K. Data on other common skin diseases, such as eczema and psoriasis were also collected but results on these diseases will be published separately. In view of links between acne and polycystic ovary syndrome (PCO) potential associations with hormone-related variables such as reproductive history, lipid metabolism [cholesterol, triglycerides, high-density lipoprotein, and apolipoprotein A1 (Apo A1)], and glucose levels were also investigated.

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Reprint requests to: Dr Veronique Bataille MD PhD FRCP, Twin Research and Genetic Epidemiology Unit, St Thomas' Hospital, London SE1 7HT, U.K. Email: vbataille@twin-research.ac.uk

## MATERIALS AND METHODS

Four hundred and fifty-eight pairs of monozygotic twins and 1099 pairs of dizygotic twins were recruited between December 1996 and January 2000.

All twins were female Caucasians with a mean age of 46 y (18–79) recruited from the St Thomas' U.K. Adult Twin Registry based in London, which is used for the study of a wide variety of common diseases (Andrew *et al*, 2001). No twin pairs belonged to the same family. Twins are recruited nationwide via media campaigns and were not aware that skin diseases or acne were being investigated prior to their visit. Zygosity of the twins was determined using a validated questionnaire (Goldsmith, 1991) and confirmed with genetic fingerprinting in ambiguous cases. The twins were interviewed using a nurse-administered questionnaire concerning several skin diseases. The skin part of this large twin study was set up to investigate the genetics of common skin diseases, including acne, eczema, and psoriasis. The results on eczema and psoriasis will be published separately. Subjects were asked whether they ever suffered from acne and if "yes" were divided into three subcategories based on the severity of their disease and the following scoring system was used in this study: (i) mild acne as self-treated by buying treatment over the counter; (ii) moderate acne as necessitating treatment by the general practitioner; and (iii) severe acne necessitating regular visits to a dermatologist. Self-reported severity of current acne has been shown to correlate well with clinical examination (Pearl *et al*, 1998). Although the study by Pearl *et al* was not a retrospective self-assessment of acne as in this study, the fact that adolescents recognize their disease and score it fairly accurately shows that acne is a well known skin disease that is amenable to self-assessment. Although all twins had a skin examination by trained nurses in our study, the prevalence of acne could not be determined by skin examination as the peak age for active acne would be much younger. All data on acne is therefore based on retrospective data from the questionnaire. All twins were asked about hair thinning as hair thinning can be a feature of PCO, which can be associated with acne; this was also assessed clinically during the skin examination that was performed by five research nurses trained for several weeks by V.B. Self-reported family history of acne in first degree relatives (not including the co-twin) was also recorded.

Data on weight, height, and reproductive factors were collected. Serum levels of fasting lipids (cholesterol, triglycerides, high-density lipoprotein, and Apo A1) were measured. Glucose levels were also collected during an oral glucose tolerance test with 75 g of glucose with serum sampling at time 0 and 120 min in a subsample of the twins. The study was approved by the St Thomas' Hospital Ethics Committee.

### Statistical analyses

**Probandwise or casewise concordance** Two by two contingency tables were used based on the presence or absence of acne in monozygotic and dizygotic twin pairs to calculate probandwise or casewise concordance using the following equation:  $2C/(2C + D)$ , where C is the number of concordant pairs (both twins having acne) and D is the number of discordant pairs. If probandwise or casewise concordance is greater in the monozygotic twins than dizygotic twins, this suggests a genetic effect on the disease. Polychoric correlations (the correlation in liability to disease among pairs of monozygotic and dizygotic twins for a categorical measure) were also calculated using acne scores from 0 to 3.

**Genetic modeling** Fitting quantitative genetic models to twin data is based on the comparison of variance-covariance (or correlation) matrices in monozygotic and dizygotic twin pairs. The observed phenotypes are assumed to be linear functions of the following four underlying components of the variance: (i) additive genetic variance (A) is the variance that results from the additive genetic effects of alleles at each contributing locus; (ii) dominant genetic variance (D) is the variance that results from the nonadditive effects of two alleles at the same locus, summed over all loci that contribute to the variance of the trait; (iii) shared or common environmental variance (C) is the variance that results from environmental events shared by both members of a twin pair; and (iv) specific or unique environmental variance (E) is the variance that results from environmental effects that are not shared by members of a twin pair, and includes measurement error (Neale, 1997; Kyvik, 2000). Further methods for heritability estimates of dichotomous traits in twins are given in the Appendix and can also be found in Millard *et al* (2000). The adjustments of heritability estimates for confounders were performed on Stata (1997, Stata Corporation, College Station, TX) using a modified DeFries Fulker regression for dichotomous traits, in which, one twin's phenotype is modeled as a logit function of their co-twin's phenotype and their zygosity (Sham *et al*, 1994).

**Cross-sectional study** Comparisons were made between acne twins (400 cases) and nonaffected twins (2414 controls). All p-values were two-sided and the level of significance was set at  $<0.05$ . General Estimating Equations were used to account for the nonindependence of data (the genetic relationship within monozygotic and dizygotic pairs) in estimating odds

ratios of being affected using Stata (Stata Corporation). Differences in family history between those with and those without were calculated using  $\chi^2$  statistics on Stata. For family history of acne in parents, siblings, and children, the comparisons were made using one twin per pair taken randomly.

**Matched co-twin case-control design** Conditional regression analysis was used to investigate potential risk factors in monozygotic and dizygotic twin pairs discordant for acne, and results were presented as odds ratios with 95% confidence intervals (95% CI). The clustering variable was the twin pair.

**Statistical software** All variance component model fitting was carried out with Mx, a software package designed for the analysis of twin data (Neale, 1997). Conditional logistic regression, General Estimating Equation,  $\chi^2$  and correlation statistics were performed on version 5 of the Stata statistical software (Stata Corporation).

## RESULTS

**Concordance for acne in monozygotic and dizygotic pairs** The prevalence of recalled acne was 14% in monozygotic twins and 14% in dizygotic twins. Age at interview was negatively associated with a reported history of acne ( $p < 0.0001$ ). Monozygotic twins were slightly older than dizygotic twins but this did not reach statistical significance ( $p = 0.055$ ). Acne scores in monozygotic and dizygotic twins are shown in **Table I** together with the mean age in each category. Acne score was not associated with zygosity ( $p = 0.9$ ) but was associated with age; 11% of the twins aged 35–50 y had scored of 2 or more (moderate to severe acne) compared with 5% in the older twins. The probandwise concordance based on two by two contingency tables for the presence or absence of acne was 0.65 in the monozygotic pairs and 0.28 in the dizygotic pairs. **Table II** shows the acne scores in twin 1 *vs* twin 2 (the co-twin). Polychoric correlations based on acne scores from 0 to 3 were 0.82 in monozygotic twins and 0.40 in dizygotic twins.

**Genetic modeling** The results of quantitative genetic analyses estimating the relative contribution of genetic and environmental factors are shown in **Table III**. The four models are based on acne scores in 4 by 4 contingency tables. The AE model (A) Additive genetic factors and (E) Unique environment model best fitted the data (**Table III**). The  $\chi^2$  obtained when comparing the ACE with (A) additive genetic + (C) common environment + (E) unique environment effect model *vs* CE model with (C) common environment + (E) unique environment was 28.4  $p < 0.0001$  showing that A could not be removed. No evidence of shared environment effects was detected and CE could be rejected. In the AE model, additive genetic effects accounted for 81% (95% CI 73–87%) of the variance for the disease with the remaining 19% (95% CI 9–27%) attributed to unique environmental effects (i.e., not shared by the twins). There was no significant evidence of dominant genetic effects but even with this large sample size our power to detect a modest influence of D was small (**Table III**). The monozygotic and dizygotic thresholds were not significantly different, which reflects the similar prevalence of acne in monozygotic and dizygotic twins.

**Table I. Age and acne scores in monozygotic (monozygotic) and dizygotic (dizygotic) pairs**

	Monozygotic	Dizygotic
Number of pairs	458	1099
Age (SD)	47.2 (13.3)	46.4 (11.7)
Prevalence of acne	14.3%	13.8%
Acne scores (mean age)		
Unaffected	85.6% (48)	86.2% (47)
Mild acne	6.3% (49)	5.1% (45)
Moderate acne	7.0% (37)	7.6% (41)
Severe acne	1.1% (43)	1.1% (44)

**Table II. Contingency tables for acne scores in monozygotic and dizygotic pairs Acne scores<sup>a</sup> for twin 1 vs twin 2 (co-twin) in monozygotic twins**

Twin 2	0	1	2	3
Twin 1				
0	374	5	9	3
1	6	21	3	0
2	10	2	19	0
3	3	0	2	1

Polychoric correlations for acne scores in monozygotic twins: 0.82.

Probandwise concordance based on 2 by 2 table for the presence or absence of acne: 0.65.

**Acne scores<sup>a</sup> for twin 1 vs twin 2 (co-twin) in dizygotic twins**

Twin 2	0	1	2	3
Twin 1				
0	850	31	58	9
1	33	18	8	1
2	53	4	21	1
3	11	0	0	1

Polychoric correlation for acne scores in dizygotic twins: 0.40.

Probandwise concordance based on 2 by 2 table for the presence or absence of acne: 0.28.

0 = unaffected; 1 = mild acne; 2 = moderate; 3 = severe acne.

Quantitative genetic analyses using Mx were repeated on 2 by 2 contingency based on the binary variable (ever acne vs never acne). The best fitting model using this definition was also AE with 91% (95% CI 84–95%) of the liability to the disease explained by additive genetic factors and the remaining 9% (95% CI 0.05–0.16) by unique environmental factors. Adjustments for covariates [age at visit, age at menarche, weight and oral contraceptive pill (OCP) use] using the modified DeFries Fulker regression on the 2 by 2 acne contingency tables did not affect the heritability estimates (data not shown). Mx analyses were also repeated on two subgroups of twins stratified for age (equal or below 50 y and above 50 y). Very similar results were obtained in both groups (data not shown) so age at interview did not affect heritability estimates.

**Cross-sectional study comparing acne twins vs nonacne twins** The comparisons between 400 acne twins and 2414 unaffected twins regarding metabolic and reproductive variables are shown in **Table IV**. Twins reporting acne were slightly younger (3.9 y) than unaffected twins but all analyses were adjusted for age and the fact that the twins are related. Birth weight, weight at age 20, current body mass index, and height were comparable between twins with and without acne. For reproductive history, twins with acne were more likely to have ever used the OCP compared with non-affected twins (93% vs 85%) and this difference reached statistical significance ( $p = 0.02$ ). The number of pregnancies was slightly but not significantly lower in acne twins. No association was found between acne and age at menarche, number of children

or history of irregular periods. Hair thinning with age was equally common in both groups. Lipid levels were slightly lower in acne twins but this difference was not significant once adjusted for age and weight except for Apo A1 ( $p = 0.05$ ). Acne scores were negatively associated with serum levels of triglycerides, cholesterol, and Apo A1, and positively associated with OCP use but these associations disappeared once adjusted for age. Glucose levels during an oral glucose tolerance test were also similar between the two groups.

Family history of acne was compared between 220 acne twins and 1358 unaffected twins (twin pairs were split with one twin taken randomly from each pair for the presence of acne in parents and siblings). Of the 220 acne twins, 47% had a family history of at least one nontwin sibling affected with acne compared with 15% in nonacne twins ( $p < 0.0001$ ). Acne affecting either or both parents was reported in 25% of the acne twins and 4% of unaffected twins ( $p < 0.0001$ ). Forty-one percent of the acne twins reported at least one child affected with acne compared with 17% of the controls ( $p < 0.0001$ ).

**Co-twin matched case-control design** The negative association between acne and Apo A1 serum levels persisted when 208 dizygotic discordant acne twin pairs were analyzed using conditional logistic regression. But this did not reach statistical significance ( $p = 0.07$ ). Contrary to the cross-sectional design, OCP use was not more common in the acne twin of dizygotic discordant twin pairs but the power to detect such a difference was limited given the widespread use of OCP in this study population. Using the small number of acne discordant monozygotic (43 pairs), no associations were found with all other potential risk factors studied in **Table IV**, including Apo A1.

## DISCUSSION

The results from this large adult twin study suggest a strong genetic basis for acne as 81% of the population variation in acne scores in U.K. adult twins was attributed to genetic factors and family history of the disease confirmed a significant familial clustering. These results are in keeping with two previous twin studies of acne that reported heritability estimates between 50 and 90% (Friedman, 1984; Kirk *et al*, 2001). Low serum levels of Apo A1 was the only significant risk factor for acne using the cross-sectional and co-twin case-control design. The results of the case-control analyses have to be taken with caution, however, as the measurements were made many years after the disease was active and possible associations with acne may have been missed because of this interval.

Possible limitations of the study need discussing: the data were retrospective and current examination of the skin for acne grading would not have been useful in view of the mean age of the twins. There is no universally accepted classification system for acne so clinical definition varies greatly between published studies (Stathakis *et al*, 1997). Nevertheless, the results of our quantitative genetic analyses were similar using our scoring grades for acne or a dichotomous classification of acne as present or absent so potential biases in recalling the severity of acne are unlikely to

**Table III. Quantitative genetic analyses based on polychoric correlations for acne scores**

Model	A (95%CI)	C/D (95%CI)	E (95%CI)	$\chi^2$	d.f.	AIC	$\Delta\chi^2$	vs	$\Delta$ d.f.	p
ACE	0.81 (0.57–0.87)	0	0.19 (0.13–0.27)	125.1	25	75.1	–			
ADE	0.79 (0.32–0.87)	0.02 (0.00–0.50)	0.19 (0.13–0.27)	125.1	25	75.1	–			
AE <sup>b</sup>	0.81 (0.73–0.87)	<sup>a</sup>	0.19 (0.13–0.27)	125.1	26	73.1	0.0	ACE	1	1
CE	<sup>a</sup>	0.57(0.49–0.64)	0.43 (0.36–0.52)	153.5	26	107.4	28.4	ACE	1	<0.001

<sup>a</sup>Component fixed to 0.

<sup>b</sup>Best fitting model with lowest AIC.

A = additive genetic variance; D = dominant genetic variance; C = common environmental variance; E = unique environment variance; d.f. = degrees of freedom; AIC = Akaike information criterion.

**Table IV. Characteristics and potential risk factors in acne twins and controls**

	Cases (SD)	Controls (SD)	Odds ratios(95%CI)	p-value
Numbers	400	2414		
Monozygotic (%)	30.3	29.3		
Dizygotic (%)	69.7	70.7		
Age (y)	43.0 (11.5)	46.9 (12.1)		
Birth weight (kg)	2.48 (0.63)	2.39 (0.60)	1.13 (0.91–1.41)	0.27
Weight at age 20 (kg)	57.06 (8.56)	56.44 (9.59)	1.00 (0.99–1.01)	0.78
Current body mass index	24.57 (4.40)	25.20 (5.06)	0.98 (0.96–1.00)	0.11
Height (cm)	163.48 (5.94)	162.52 (6.49)	1.00 (0.99–1.03)	0.28
Age at menarche (y)	12.85 (1.55)	12.98 (1.58)	0.96 (0.90–1.03)	0.27
Menstrual cycle length (d)	27.78 (2.8)	27.96 (3.13)	1.00 (0.97–1.05)	0.68
Number of pregnancies	1.87 (1.59)	1.94 (1.63)	1.05 (0.95–1.15)	0.21
Number of children	1.54 (1.2)	1.70 (1.52)	0.99 (0.92–1.09)	0.99
Irregular periods (%)	14.4	12.6	1.20 (0.88–1.66)	0.24
OCP use ever (%)	15.0	6.5	1.75 (1.08–2.08)	0.02
Hair thinning (%)	11.7	11.4	1.13 (0.76–1.68)	0.56
Cholesterol (mmol per l)	5.27 (1.23)	5.53 (1.25)	1.01 (0.91–1.13)	0.81
Triglycerides (mmol per l)	1.09 (0.60)	1.22 (0.73)	0.85 (0.70–1.04)	0.12
High-density lipoprotein (mmol per l)	1.53 (0.36)	1.55 (0.40)	0.89 (0.65–1.23)	0.43
Apolipoprotein A1 (g per l)	1.63 (0.34)	1.67 (0.47)	0.71 (0.51–1.00)	0.05
Fasting glucose	4.43 (0.76)	4.56 (0.95)	0.86 (0.72–1.03)	0.09
2 h glucose (oral glucose tolerance test) <sup>a</sup>	5.23 2.06	5.25 (1.38)	1.03 (0.95–1.14)	0.42

All odds ratios are adjusted for age and twin dependency apart from cholesterol, triglycerides, high-density lipoprotein, Apo A1, fasting glucose, and 2 h glucose for which the odds ratios were adjusted for age, twin dependency and current weight.

<sup>a</sup>Available in 191 cases and 1073 controls.

have had a major effect on the heritability. Moreover, the questionnaire was administered by the same nurse for both twins with identical questions on many different diseases, which should have limited any systematic recall bias. Both twins were always seen on the same day with identical protocols and were not aware that skin diseases were being investigated prior to the interview. Acne is a well known skin disease and its characteristic clinical features render it difficult to be confused with other skin disorders affecting the face in adolescence or early adulthood. Whereas acne prevalence did decrease with age, which may suggest poorer recall in older twins this did not affect the heritability estimates as this poorer recall should not be significantly and systematically different in monozygotic *vs* dizygotic pairs. This is supported by the fact that the age-specific prevalence of acne was comparable in monozygotic and dizygotic pairs, and also by the similar estimates of the genetic effect in younger and older twins. The difference in self-reported acne according to age could also be explained by an increase in acne prevalence or acne awareness over the last 30 y. There was also no association between zygosity and acne score, which support the fact that monozygotic and dizygotic recalled their disease in the same way. The overall prevalence of acne in this study is comparable with other population-based studies in adults and only slightly lower than the prevalence of acne in the twin study reported by Friedman (Cunliffe, 1975; Friedman, 1984; Maisonneuve *et al*, 1987; Rade-maker *et al*, 1989; Chua-Ty *et al*, 1992; Kilkenny *et al*, 1998; Goulden *et al*, 1999b; Aktan *et al*, 2000). Whereas other studies in adolescents have reported prevalence between 50% and 80%, these studies included grade 1 and grade 2 of acne according to the Leeds Acne Grading system, which are defined by a few comedones and/or few papules that may not be recalled by our adult population (Burton *et al*, 1971; Smithard *et al*, 2001). This study is therefore likely to concentrate on the moderate to severe grades of acne (grade 3 and above of the Leeds Grading System) as very mild and mild acne grades are almost universal in adolescents with no significant psychologic morbidity. Family history was again dependent on the twin's recall; however, family data is in keeping with other population-based acne studies (Goulden *et al*, 1999a,b). In a recent U.K. study, acne was four times more common in first degree relatives of 204 acne cases than first degree relatives of 144 controls (Goulden *et al*, 1999b).

The twin method is considered to be the optimal method to separate the relative contribution of genetic and environmental factors on a trait or disease as familial clustering from family studies can, in part, be explained by shared environmental factors that are difficult to dissect from the genetic influence (Martin *et al*, 1997; Kyvik, 2000). Estimates of heritability can be biased if greater sharing of environmental confounders strongly related to the disease occurs more commonly in the monozygotic pairs compared with dizygotic pairs. We have, however, adjusted the heritability estimates for possible confounders in this study and these did not significantly affect the estimates. This twin study shows that the familial clustering observed is due to strong genetic effects and not shared environment.

The pathology of acne is found in the pilosebaceous unit with increased activity of the sebaceous glands, faulty cornification, microbial colonization of the follicular channel and inflammatory dermal reaction in response to the obstruction of the follicle (Gollnick *et al*, 1991). Studies investigating the morphologic and immunologic profile of the sebaceous unit have so far failed to discover initiating factors for this disease (Harris *et al*, 1983; Downing *et al*, 1986). The role of the skin bacteria, *Propionibacterium acnei*, in acne is not clear, although this organism and the fatty acids produced in the blocked follicles contribute to the inflammatory process (Webster *et al*, 1982; Leyden *et al*, 1983; Holland *et al*, 1998).

Hormonal factors (endogenous or exogenous) are thought to play an important part in acne in view of the onset of the disease around puberty, the relationship between acne and hyperandrogenism and the therapeutic effect of anti-androgenic agents. Furthermore, an association between PCO and acne has also long been established (Sheehan *et al*, 1988; Rosenfield, 1986; Betti *et al*, 1990). In this study based on a large U.K. population-based sample, none of the reproductive or hormonal potential risk factors studied were found to be associated with acne apart from OCP use. Rather than being causal, this association is likely to be explained by the fact that OCP is one of the therapeutic options for acne. Moreover, in the analyses of discordant dizygotic and monozygotic pairs, OCP use was not significant. Hair thinning (male pattern baldness), which can be a feature of PCO, was not more common in acne twins in this study. The association between acne and raised androgen levels has been controversial

as some studies have reported increased levels of both total and free androgens in acne, whereas others have reported androgen levels within normal limits and no correlations between acne severity scores and testosterone levels (Forstrom *et al*, 1974; Steinberger *et al*, 1981; Darley *et al*, 1982; Lucky *et al*, 1983; Marynick *et al*, 1983; Schiavone *et al*, 1983; Ginsberg *et al*, 1986; Lawrence *et al*, 1986; Levell *et al*, 1989; Ramsay *et al*, 1995). In this study, serum testosterone levels were only available in a very small subset of twins (data not shown) and were not informative because of low power.

PCO linked to acne affects 2–20% of the normal population depending on the definition used and also appears to cluster in families with an autosomal mode of inheritance (Knochenhauer *et al*, 1998; Franks *et al*, 1998; Kashar-Miller and Azziz, 1999; Urbanek *et al*, 1999). Women suffering from PCO not only have high levels of androgens but also insulin resistance with hyperinsulinaemia as well as raised serum lipids. In the twin study reported here, Apo A1 serum levels were lower in acne twins and this is in keeping with lipid changes previously reported in women with PCO (Lithell *et al*, 1987). This difference in Apo A1 was also found when analyzing acne discordant dizygotic pairs, although this did not reach statistical significance. This difference in Apo A1 between acne subjects and controls needs to be confirmed in other populations and in adolescents. The difference in Apo A1 was not found in the monozygotic acne discordant twin pairs but the number of discordant monozygotic pairs was small. Weight and glucose levels were similar between acne twins and nonacne twins.

In conclusion, this study using the twin model confirms that acne is a highly heritable disease with significant additive genetic effects. The strong genetic basis should stimulate more research leading to gene discovery for this common and often disabling disease. So far, few acne candidate genes have been proposed, some of them related to androgen and steroid metabolism, although sample sizes were small (Blanche *et al*, 1997; Ando *et al*, 1998; Munro and Wilkie, 1998; Paraskevidis *et al*, 1998; Sawaya and Shalita, 1998). The lack of research in the genetics of acne is surprising considering its incidence, morbidity, and health service costs. Acne is currently treated with keratolytics, topical and systemic antibiotics, anti-androgens as well as topical retinoids, which have different targets with complementary effects on infection, inflammation, sebum secretion rate, and follicular duct keratinization. For severe acne with scarring, oral retinoids have been a major breakthrough in the management of this disease but have significant side-effects with the added concern of teratogenicity. New therapeutic options for all grades of acne, early treatment for genetically susceptible individuals as well as new drugs specifically targeted at genetic pathways would be welcomed. The understanding of the genetics of this common disease may also unravel genes that may have pleiotropic effects on other related phenotypes such as lipid metabolism.

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## APPENDIX

The genetic model can be represented by the following linear structural equations: (1)  $P_i = aA_i + dD_i + cC_i + eE_i$  and (2)  $V_P = a^2 + d^2 + c^2 + e^2$ , where  $P$  is the phenotype of the  $i$ th individual scaled as a deviation from zero.

The modeling analyses were based on 4 by 4 contingency tables for acne scores for monozygotic and dizygotic pairs, respectively. Models were fitted by the method of maximum likelihood using Mx software (Neale, 1997). The relative significance of A, C, and D is tested by removing them sequentially in specific sub-

models by hierarchic  $\chi^2$ -tests, in which the  $\chi^2$ -value of a submodel is subtracted from that of the full model. The differences in  $\chi^2$ -values between different models is itself approximately distributed as  $\chi^2$  and the degree of freedom are equal to the difference between the degrees of freedom for the full model and the submodel. The best fit is evaluated on the basis of the  $\chi^2$ , the p-value and the Akaike's Information Criterion: the model with the lowest Akaike's Information Criterion and highest p-value reflects the best balance of goodness of fit and parsimony. The p-value refers to the goodness of fit statistic. The higher the p-value the closer the data to the model, the lower the p-value the poorer the fit.

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