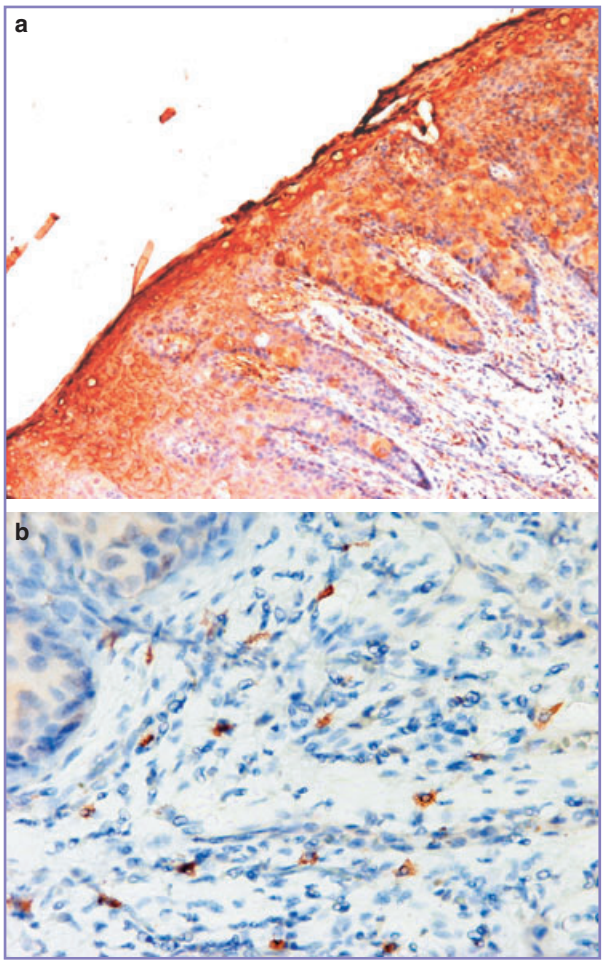

Fig 1. (a) Immunohistochemical staining for elafin in extramammary Paget's disease (EMPD). The intensity of staining is greatest in the granular layer. Almost all of the Paget cells were strongly positive. (b) Interferon-γ-positive cells (brown) in the upper dermis of EMPD.

infiltrates. We therefore examined the expression of IFN-γ in the dermal infiltrates.[8] As expected, there was a large number of IFN-γ-positive cells in the dermal infiltrates in EMPD (Fig. 1b). The biological significance of elafin expression is not known, but it may be involved in the protection of tumour cells from extensive destruction via immune reaction.[9]

Department of Dermatology, Graduate School of Medical Sciences, Kyushu University, Maidashi 3-1-1, Higashiku, Fukuoka 812–8582, Japan
H-J. Liu‡
Y. Moroi
S. Yasumoto*
T. Koga
T. Masuda
Q-J. Chen
Y-T. Tu‡
M. Furue
H. Aburatani†
K. Urabe
**Department of Dermatology, Kurume University, Kurume, Fukuoka, Japan*
†Genomescience Division, RCAST, University of Tokyo, Tokyo, Japan
‡Department of Dermatology, Union Hospital, Tongji Medical College, Wuhan, Hubei, China
Correspondence: Kazunori Urabe.
E-mail: kaurabe@dermatol.med.kyushu-u.ac.jp

References

1 Molhuizen HO, Alkemade HA, Zeeuwen PL *et al.* SKALP/elafin: an elastase inhibitor from cultured human keratinocytes. Purification, cDNA sequence, and evidence for transglutaminase cross-linking. *J Biol Chem* 1993; **268**:12028–32.
2 Schalkwijk J, van Vlijmen IM, Alkemade HA *et al.* Immunohistochemical localization of SKALP/elafin in psoriatic epidermis. *J Invest Dermatol* 1993; **100**:390–3.
3 van Bergen BH, Andriessen MP, Spruijt KI *et al.* Expression of SKALP/elafin during wound healing in human skin. *Arch Dermatol Res* 1996; **288**:458–62.
4 Alkemade HA, van Vlijmen-Willems IM, van Haelst UJ *et al.* Demonstration of skin-derived antileukoproteinase (SKALP) and its target enzyme human leukocyte elastase in squamous cell carcinoma. *J Pathol* 1994; **174**:121–9.
5 Alkemade HA, Molhuizen HO, van Vlijmen-Willems IM *et al.* Differential expression of SKALP/elafin in human epidermal tumors. *Am J Pathol* 1993; **143**:1679–87.
6 Westin U, Nystrom M, Ljungcrantz I *et al.* The presence of elafin, SLPI, IL1-RA and sTNFalpha RI in head and neck squamous cell carcinomas and their relation to the degree of tumour differentiation. *Mediators Inflamm* 2002; **11**:7–12.
7 Pfundt R, Wingens M, Bergers M *et al.* TNF-alpha and serum induce SKALP/elafin gene expression in human keratinocytes by a p38 MAP kinase-dependent pathway. *Arch Dermatol Res* 2000; **292**:180–7.
8 Koga T, Duan H, Urabe K, Furue M. *In situ* localization of IFN-gamma-positive cells in psoriatic lesional epidermis. *Eur J Dermatol* 2002; **12**:20–3.
9 Pfundt R, van Ruissen F, van Vlijmen-Willems IM *et al.* Constitutive and inducible expression of SKALP/elafin provides anti-elastase defense in human epithelia. *J Clin Invest* 1996; **98**:1389–99.

Conflicts of interest: none declared.

Teenage acne is influenced by genetic factors

DOI: 10.1111/j.1365-2133.2005.06387.x

Sir, Acne vulgaris is a common inflammatory disease of the pilosebaceous glands characterized by inflamed (papules, pustules, nodules and cysts) and noninflamed lesions (comedomes) on the face, neck, chest and back. The prevalence of acne in adolescents has been reported as being between 35% and 90%, depending on the method of classification, with peak incidence occurring at between 14 and 17 years in females, and 16 and 19 years in males.[1,2] As well as the physical pain and discomfort that acne produces, it is well documented that acne sufferers experience higher levels of psychological distress, are more self-conscious and have a poorer self-image than age-matched controls. A possible role for genetic factors in the development of acne is based on the observation that relatives of affected individuals are at increased risk of developing acne compared with unrelated individuals. However, relatives share similar environments as well as genes. We can test the hypothesis that genetic factors

affect the development of acne more rigorously by using the classical twin design which compares the similarity of monozygotic (MZ) twin pairs with that of dizygotic (DZ) twin pairs. Assuming that MZ and DZ twins experience the same degree of environmental similarity, any excess similarity between MZ pairs relative to DZ pairs must be the result of genetic factors. Previous twin studies have suggested a role for genetic factors in the development of acne,[3–5] although most of these studies have involved retrospective reports from adult twins. Until now there has been no prospective study of acne development in a large sample of twins during adolescence when this skin disease is most prevalent.

We rated the severity of acne at three sites (face, chest, back) in 778 pairs of twins longitudinally at ages 12 and 14 years and on the face only at age 16 years. Not all twins were measured at each age (Table 1). Severity of acne was judged by a nurse using a four-point scale (0, absent; 1, mild; 2, moderate; 3, severe). The validity of our scale was confirmed by a dermatologist (C.N.) who rated photographs of 40 twin pairs using our scale and the internationally accepted Leeds scale of acne severity (Spearman's correlation = 0·951). The proportion of individuals in each category of severity was very similar to that reported in a previous study of acne involving Australian adolescents.[2] Twin zygosity was determined by typing eight highly polymorphic DNA microsatellite markers. Phenotypic variation in acne severity was decomposed into variance resulting from additive genetic (A), common environmental (C) and unique environmental (E) sources using a structural equation modelling approach. Estimates of A, C and E were obtained by maximum-likelihood analysis of individual observations on the assumption that each category of severity reflected the imprecise measurement of an underlying continuous normal distribution of liability which had a number of thresholds discriminating between the ordered phenotypic categories.[6] For some variables it was necessary to collapse data to three or even two categories because of the

Table 1 Number of twin individuals (n) and frequency (%) of boys and girls with no (0), mild (1), moderate (2) and severe (3) acne at ages 12, 14 and 16 years, as rated longitudinally by nurses

			Severity											
			Face				Chest				Back			
Age (years)	Sex	n	0	1	2	3	0	1	2	3	0	1	2	3
12	F	586	57·8	32·3	7·2	2·7	93·0	6·0	0·9	0·2	88·6	8·0	2·7	0·7
12	M	585	80·9	17·1	1·0	1·0	98·6	1·0	0·2	0·2	97·6	1·9	0·2	0·3
14	F	478	17·8	51·3	19·9	11·1	74·9	19·5	4·8	0·8	64·0	23·2	10·7	2·1
14	M	470	30·1	47·4	16·4	5·3	88·7	9·1	1·1	1·1	78·3	14·3	5·7	1·7
16	F	424	35·8	43·6	15·6	5·0	–	–	–	–	–	–	–	–
16	M	406	19·7	50·7	24·1	5·4	–	–	–	–	–	–	–	–

Table 2 Number of complete twin pairs, polychoric correlations and standardized variance components of acne severity by zygosity group, site and age

		Polychoric correlations					Standardized variance components (95% confidence intervals)		
Age (years)		MZF	MZM	DZF	DZM	DZO	A	C	E
12	n_{pairs}	105	103	97	99	181			
	Face	0·88	0·73	0·63	0·26	0·14	0·83 (0·72–0·91)	–	0·17 (0·09–0·28)
	Chest[a]	0·95			0·61		0·55 (0·34–0·88)	0·42 (0·09–0·63)	0·03 (0·00–0·10)
	Back[a]	0·97			0·59		0·97 (0·91–1·0)	–	0·03 (0·00–0·09)
14	n_{pairs}	96	85	74	81	138			
	Face[b]	0·80	0·79	0·53	0·31	0·08	0·78 (0·63–0·87)	–	0·22 (0·13–0·37)
	Chest	0·95	0·79	0·45	0·60	0·10	0·91 (0·58–0·97)	–	0·09 (0·03–0·20)
	Back	0·90	0·92	0·64	0·41	0·25	0·91 (0·60–0·94)	–	0·09 (0·06–0·15)
16	n_{pairs}	100	91	56	56	112			
	Face	0·90	0·82	0·30	0·44	0·36	0·86 (0·80–0·90)	–	0·14 (0·10–0·20)

MZF, monozygotic female; MZM, monozygotic male; DZF, dizygotic female; DZM, dizygotic male; DZO, dizygotic opposite-sex; A, additive genetic sources; C, common environmental sources; E, unique environmental sources. [a]Polychoric correlations for acne on the chest and back at age 12 years were pooled over sexes because of small cell sizes. [b]Variance components for males are shown. Variance components for females were A = 0·31 (0·01–0·67), C = 0·46 (0·13–0·71), E = 0·22 (0·14–0·36).

small number of cases in the higher categories. Thresholds did not differ across birth orders or zygosities, although girls had more severe acne than boys at all sites at both 12 and 14 years, but not at 16 years, when acne was more severe in boys ($P < 0{\cdot}001$ in all cases). Thus, separate thresholds for boys and girls were maintained for subsequent analyses.

Genetic factors explained significant proportions of the variation in acne severity at all sites and ages, contributing from 31% to 97% of the phenotypic variance (Table 2). In particular, heritability of acne on the back was very high. Interestingly, at age 14 years, facial acne in girls was less influenced by genetic factors than in boys, and was significantly influenced by common environmental factors. Common environmental factors also significantly affected the severity of acne on the chest of 12-year-olds. Why should common environmental factors influence acne severity at some sites and ages but not others? We note that there is low power to detect common environmental effects using information from twins alone.[7] This is due in part to the high correlation between estimates of A and C using this methodology.[8] In other words, it is possible that common environmental factors may have influenced acne severity (e.g. antiacne medications), but that in most cases the present study had inadequate power to resolve this component from additive genetic influences. The results in Table 2 lend some support to this hypothesis, as in many cases the correlation between same-sex DZ twins was greater than half the corresponding MZ correlation (i.e. suggesting common environmental influences). In contrast, the correlation between opposite-sex DZ twin pairs was very low in most cases. Including opposite-sex twins in the analyses would have decreased the total DZ correlation and thus the evidence for common environmental factors.

However, the major finding from our study was that the severity of acne at all sites and ages was strongly influenced by genetic factors. The task now is to identify the individual genes responsible for this high heritability. We are currently performing a genome scan in an effort to identify these individual loci.

Acknowledgments

Collection of phenotypes and DNA samples was supported by grants from the Queensland Cancer Fund, the Australian National Health and Medical Research Council (950998, 981339 and 241944) and the U.S. National Cancer Institute (CA88363) to Dr Nick Hayward. We thank our research nurses Ann Eldridge and Marlene Grace for assistance and the twins and their parents for their cooperation.

*Queensland Institute of Medical Research, Brisbane, Australia
†Wellcome Trust Centre for Human Genetics, University of Oxford, Roosevelt Drive, Oxford OX3 7BN, U.K.
‡Dermatology Outpatients, Royal Brisbane Hospital, Brisbane, Australia
E-mail: davide@well.ox.ac.uk

D.M. Evans*†
K.M. Kirk*
D.R. Nyholt*
C. Novac‡
N.G. Martin*

References

1 Stathakis V, Kilkenny M, Marks R. Descriptive epidemiology of acne vulgaris in the community. *Australas J Dermatol* 1997; **38**:115–23.
2 Kilkenny M, Merlin K, Plunkett A, Marks R. The prevalence of common skin conditions in Australian school students: 3. Acne vulgaris. *Br J Dermatol* 1998; **39**:840–5.
3 Friedman GD. Twin studies of disease heritability based on medical records: application to acne vulgaris. *Acta Genet Med Gemellol* 1984; **33**:487–95.
4 Walton S, Wyatt EH, Cunliffe WJ. Genetic control of sebum excretion and acne—a twin study. *Br J Dermatol* 1988; **118**:393–6.
5 Bataille V, Sneider H, MacGregor AJ *et al*. The influence of genetics and environmental factors in the pathogenesis of acne: a twin study of acne in women. *J Invest Dermatol* 2002; **119**:1317–22.
6 Neale MC, Cardon LR. *Methodology for Genetic Studies of Twins and Families*. Dordrecht: Kluwer Academic Publishers, 1992.
7 Martin NG, Eaves LJ, Kearsey MJ, Davies P. The power of the classical twin study. *Heredity* 1978; **40**:97–116.
8 Williams CJ. On the covariance between parameter estimates in models of twin data. *Biometrics* 1993; **49**:557–68.

Conflicts of interest: none declared.

Successful treatment of chronic ulcerated necrobiosis lipoidica with 0·1% topical tacrolimus ointment

DOI: 10.1111/j.1365-2133.2005.06388.x

Sir, Necrobiosis lipoidica (NL) is a recognized cutaneous manifestation of type 1 diabetes mellitus. It often proves recalcitrant to treatment and may ulcerate. NL is a degenerative disease of collagen within the mid- and lower dermis and subcutaneous fat. Its aetiology is still unknown, although various possible mechanisms have been implicated. A T-cell-mediated hypersensitive immune reaction with release of proinflammatory cytokines and lysosomal enzymes leading to local tissue destruction with inflammation has been suggested.[1] Tacrolimus has recently been shown to be effective in patients with a short history of granuloma annulare (GA) or NL, and whose disease is still at the early acute inflammatory stage without any granulomatous tissue reaction.[2] Several therapies have also been reported to be successful in patients with NL, including topical and systemic corticosteroids,[3,4] ciclosporin,[1] pentoxifylline[5] and topical psoralen plus ultraviolet A (PUVA).[6] We report a 62-year-old diabetic woman with chronic NL, in whom the ulceration due to NL responded to 0·1% topical tacrolimus.

A 62-year-old woman presented to our department with a 6-month history of a progressive inflammatory eruption on her lower limbs. She was known to have rheumatoid arthritis and hypothyroidism, and was a nonsmoker. Examination revealed discrete purple atrophic plaques on her shins and upper arms, consistent with NL. There was evidence of