

# The Heritability of Polymorphic Light Eruption

Thomas P. Millard,\* Veronique Bataille,\*‡ Harold Snieder,‡ Tim D. Spector,‡ and Jane M. McGregor\*†

\*St John's Institute of Dermatology, London, U.K.; †Department of Dermatology, Royal London Hospital, London, U.K.; ‡Twin Research and Genetic Epidemiology Unit, St Thomas' Hospital, London, U.K.

**Polymorphic light eruption is classified as an acquired idiopathic photodermatosis, yet it appears to cluster in families, suggesting a possible genetic component. In this study, we assess the heritability of polymorphic light eruption using the classical twin model. Polymorphic light eruption was investigated by a nurse-administered questionnaire in a sample of 420 pairs of adult female twins from St Thomas' Hospital UK Adult Twin Registry, including 119 monozygotic and 301 dizygotic pairs. Probandwise concordance for the presence and absence of disease was calculated and the heritability of polymorphic light eruption assessed by a quantitative genetic model fitting approach using Mx software. The prevalence of polymorphic light eruption was 21% and 18% in monozygotic and dizygotic twins, respectively. A family history of polymorphic light eruption in first-degree relatives (not including the cotwin) was present in 12% of affected twin pairs (where at least one twin had polymorphic light eruption) compared with 4% of unaffected twin pairs,**

**providing evidence of familial clustering ( $p < 0.0001$ ). The probandwise concordance for polymorphic light eruption was higher in monozygotic (0.72) than in dizygotic twin pairs (0.30), indicating a strong genetic effect. Quantitative genetic modeling found that a model comprising additive genetic (A) and unique environmental (E) factors provided the most parsimonious fit, although a dominant gene effect could also explain our data. In the AE model, 84% (95% confidence interval 65–94%) of the variance in susceptibility to polymorphic light eruption is attributed to additive genetic factors with the remaining 16% (95% confidence interval 6–35%) to unique environmental effects. These data establish a clear genetic influence in the expression of polymorphic light eruption and provide a basis for examining candidate genes that may be pathogenic in this common condition. *Key words: genetic modeling/photosensitivity/polymorphic light eruption/twins. J Invest Dermatol 115:467–470, 2000***

**P**olymorphic light eruption (PLE) is the most common of the so-called idiopathic photodermatoses. In a recent population survey in the U.K., PLE was found to affect 15% of healthy people, with a female to male ratio of approximately 2:1 (Pao *et al*, 1994). PLE is characterized by transient, nonscarring pruritic papules and vesicles, typically developing hours or days after sun exposure and resolving over several days without sequelae. It is often mild, occurring only on summer holidays; however, PLE can occasionally be incapacitating, sometimes requiring treatment with systemic steroids.

The pathogenesis of PLE is unclear, but some evidence suggests that it may be a hypersensitivity reaction to an antigen induced or upregulated in the skin following exposure to ultraviolet radiation (UVR) (Norris *et al*, 1992). Although classified as an "acquired" idiopathic condition, a family history of PLE has been reported in almost 50% of cases, suggesting a possible genetic component (Ros and Wennersten, 1986); however, familial clustering may arise as a

result of a shared environmental background, with or without shared genetic factors. In PLE, the relative importance of these factors has not previously been investigated. In this study we use the twin model to examine the heritability of PLE, which provides an effective means of quantifying the contribution of genetic and environmental factors in disease expression.

## MATERIALS AND METHODS

**Data source** Four hundred and twenty consecutive pairs of female twins were recruited from St Thomas' Hospital UK Adult Twin Registry via a national media campaign by the unit. Twins were unaware of the specific hypotheses being tested and were enrolled for the study of a wide variety of diseases and traits. All subjects answered a series of nurse-administered questionnaires in the twin unit, covering 500 health-related questions. The photosensitivity section of the questionnaire comprised a series of questions that were designed to evaluate symptoms of PLE in twins and their first-degree relatives. Zygosity of the twins was determined using a validated questionnaire (Goldsmith, 1991), confirmed with multiplex DNA fingerprinting using variable tandem repeats (Jeffreys *et al*, 1985).

## Analytical approach

**Prevalence and familial clustering** The prevalence of PLE in our sample of monozygotic (MZ) and dizygotic (DZ) twins was calculated as a percentage of individual twins ever affected in each group. Familial clustering was then estimated by comparing the PLE prevalence in first-degree relatives of affected (where at least one twin had PLE) versus unaffected twin pairs (excluding the co-twin and irrespective of zygosity) by  $\chi^2$ -test.

Manuscript received December 8, 1999; revised May 16, 2000; accepted for publication June 13, 2000.

Reprint requests to: Dr. J.M. McGregor, Department of Photobiology, St John's Institute of Dermatology, St Thomas' Hospital, London, SE1 7EH, U.K. Email: thomas.millard@kcl.ac.uk.

Abbreviations: PLE, polymorphic light eruption; MZ, monozygotic; DZ, dizygotic; PWC, probandwise concordance; AIC, Akaike's information criterion;  $r$ , tetrachoric correlation;  $V_p$ , phenotypic variance; A, additive genetic effect; D, dominant genetic effect; C, common environmental effect; E, unique environmental effect.

**Probands concordance** Contingency tables for the presence and absence of PLE in both MZ and DZ twin pairs were constructed (Tables I and II) and probands concordance (PWC, also known as casewise concordance) calculated for both sets of twins. This describes the probability that if one twin is affected, the cotwin will also be affected. If the PWC is higher in MZ than DZ pairs, a heritable effect is indicated. PWC is derived directly from the 2 × 2 contingency tables using the following equation:

$$2C / (2C + D)$$

where C is the number of concordant pairs and D is the number of discordant pairs.

**Genetic modeling** Quantifying the genetic and environmental contribution to a dichotomous variable, such as the presence or absence of PLE, is possible by assuming that there is a continuous, underlying liability to disease (Falconer, 1989) and that a threshold of liability divides subjects into two categories: affected and unaffected. Multiple genetic and environmental factors are assumed to contribute to the variance of the liability distribution. In samples of twins, the correlation in liability among twins (the tetrachoric correlation) can be estimated from the frequencies of concordant and discordant pairs if it is assumed that the underlying liability follows (or can be transformed to) a normal distribution. Structural modeling methods can then be applied to the MZ and DZ twin correlations to provide estimates of the relative contribution of genetic and environmental factors to the variance in liability to PLE (Neale and Cardon, 1992).

Genetic variance includes an additive component (A) and a dominant component (D). Additive genetic variance is the variance that results from the additive effects of alleles at each contributing locus. Dominant genetic variance represents the nonadditive effects of two alleles at the same locus summed over all loci that contribute to the variance of the trait. Environmental variance in twins is divided into a component that is common to both members of the twin pair [the shared or common environmental variance (C)] and the variance due to random, unique environmental effects (E).

The genetic model can be represented by the following linear structural equations:

$$P = aA_i + dD_i + cC_i + eE_i \tag{1}$$

$$V_p = a^2 + d^2 + c^2 + e^2 = 1 \tag{2}$$

where P is the phenotype of the *i*th individual, scaled as a deviation from zero.  $V_p$  is the total phenotypic variance of the population, representing the sum of the individual components,  $a^2$  (additive genetic variance),  $d^2$

(dominant genetic variance),  $c^2$  (common environmental variance) and  $e^2$  (unique environmental variance) (Snieder *et al*, 1997). A, D, C, and E can be conceived of as uncorrelated latent factors with zero mean and unit variance; a, d, c, and e are regression coefficients of the observed variable on the latent factors and they indicate the degree of relationship between latent factors and the phenotype. Squaring the regression coefficients yields the variance components ( $V_A = a^2$ ,  $V_D = d^2$ ,  $V_C = c^2$ ,  $V_E = e^2$ ) whose sum is equal to the total phenotypic variance, which is 1 for threshold traits.

For MZ twins, correlations between additive and dominant genetic factors between the twin and cotwin are unity. For DZ twins, these values are 0.5 and 0.25, respectively. By definition, in both MZ and DZ same-sex pairs, correlations are unity between common environmental factors and zero between unique environmental factors. The observed tetrachoric correlations can therefore be represented as the sum of the following components for MZ and DZ twins, respectively:

$$r_{MZ} = a^2 + c^2 + d^2$$

$$r_{DZ} = \frac{1}{2}a^2 + c^2 + \frac{1}{4}d^2$$

where  $r_{MZ}$  and  $r_{DZ}$  are the tetrachoric correlations.

In our analysis, all models used data in the form of 2 × 2 contingency tables, in which the cells contained the frequencies of pairs concordant and discordant for the presence or absence of PLE in the MZ and DZ twins. Models were fitted to these matrices by the method of maximum likelihood (Neale, 1997) and the relative significance of A, C, and D tested by removing them sequentially in specific submodels by hierarchic  $\chi^2$ -tests; the  $\chi^2$ -value of a submodel is subtracted from that of the full model. The degrees of freedom (d.f.) for this test are equal to the difference between the d.f. for the full model and the submodel.

The reconstructed 2 × 2 data from each of these models were compared with the observed twin data (i.e., the original 2 × 2 tables) and  $\chi^2$ -values, p-values, and Akaike's Information Criterion (AIC,  $\chi^2 - 2$  d.f.) generated to evaluate the fit of the models. The model with the lowest AIC reflects the best balance of goodness of fit and parsimony (Neale and Cardon, 1992). A low  $\chi^2$  and a high p-value indicate that the model offers a good description of the data. Each model also produces parameter estimates for each of the tested variance components. The aim of the model fitting procedure is to obtain the simplest model that provides an adequate description of the data (i.e., the best-fitting model). The heritability ( $h^2$ ) for the best-fitting model is defined as the proportion of phenotypic variance attributed to the sum of the additive and dominant genetic variance ( $h^2 = a^2 + d^2$ ).

**Statistical software** All model fitting was carried out with Mx, a software package specifically designed for the analysis of genetically informative data (Neale, 1997). The contingency tables, prevalence figures, and PWC were constructed using STATA software (StataCorp, 1997).

RESULTS

**Demographics and prevalence data** Four hundred and twenty female twin pairs comprised 119 MZ and 301 DZ pairs with mean ages of 52 and 45 y, respectively (range: 19–73 y). The prevalence of PLE was 21% in MZ and 18% in DZ twins.

**Familial clustering** PLE in one or more first-degree relatives (excluding the co-twin) was present in 12% of affected twin pairs (where one or both twins had ever had PLE) compared with 4% of unaffected twin pairs, providing evidence of familial clustering ( $p < 0.0001$ ).

**Concordance analysis** Tables I and II are contingency tables for MZ and DZ twins, respectively. One hundred and five of 119 (88%) MZ pairs were concordant for the presence or absence of PLE, compared with 226 of 301 (75%) DZ pairs. PWC for MZ and DZ twins was calculated as 0.72 and 0.30, respectively, providing strong evidence of a genetic influence in disease expression. This was then quantified by model fitting.

**Genetic modeling** The tetrachoric correlation for MZ twins ( $r_{mz} = 0.87$ ) was higher than for DZ twins ( $r_{dz} = 0.28$ ), indicating a strong genetic effect. The results of model-fitting to the data are shown in Table III. Three sequences of nested models were examined:

**Table I. Contingency table for monozygotic twins**

	Twin 2		Total
	No PLE	PLE	
Twin 1			
No PLE	87	6	93
PLE	8	18	26
Total	95	24	119

$$\text{Probands concordance} = \frac{2 \times 18}{(2 \times 18) + 8 + 6} = 0.72$$

$r_{mz} = 0.87$

**Table II. Contingency table for dizygotic twins**

	Twin 2		Total
	No PLE	PLE	
Twin 1			
No PLE	210	41	251
PLE	34	16	50
Total	244	57	301

$$\text{Probands concordance} = \frac{2 \times 16}{(2 \times 16) + 34 + 41} = 0.30$$

$r_{dz} = 0.28$

**Table III. Modeling results for the concordance data**

	a <sup>2</sup>	c <sup>2</sup> /d <sup>2</sup>	e <sup>2</sup>	χ <sup>2</sup>	d.f.	p	AIC
ACE	0.84 [0.53–0.94]	0.00 [0.00–0.23]	0.16 [0.06–0.35]	3.38	3	0.34	–2.62
ADE	0.28 [0.00–0.92]	0.59 [0.00–0.95]	0.13 [0.05–0.30]	1.71	3	0.63	–4.29
AE	0.84 [0.65–0.94]	–	0.16 [0.06–0.35]	3.38	4	0.50	–4.62
CE	–	0.52 [0.35–0.66]	0.48 [0.34–0.65]	17.94	4	0.001	9.94
E	–	–	1.0 [1.0–1.0]	50.86	5	<0.001	40.86

Critical value for χ<sup>2</sup> (d.f. = 1) = 3.84.

Critical value for χ<sup>2</sup> (d.f. = 2) = 5.99.

a<sup>2</sup>, Additive genetic variance; d<sup>2</sup>, dominant genetic variance; c<sup>2</sup>, common environmental variance; e<sup>2</sup>, unique environmental variance.

ACE↔AE↔E

ACE↔CE↔E

ADE↔AE↔E

All models that included a genetic component provided a significantly better fit than environmental models (CE and E). Considering the genetic-based models in turn, removing C from ACE generated the same χ<sup>2</sup>-value (3.38); thus C (shared environment) is not a significant component in our PLE model. Conversely, when A was removed from the ACE model, the χ<sup>2</sup> increased significantly from 3.38 to 17.94, indicating that A is an important contributor. Comparing ADE with AE similarly, the χ<sup>2</sup> increased from 1.71 to 3.38, but the difference in χ<sup>2</sup> (1.67) is not significant. For 1 d.f., the difference in χ<sup>2</sup> between the two models must be greater than the critical value of 3.84 to provide significance at the 0.05 level. The submodel that involved the environmental component E alone had the largest χ<sup>2</sup>-value, i.e., showed the worst fit to the data.

To summarize, both the AE and ADE models provide an adequate fit to the data. The “best fit” model, however, with the lowest AIC is the AE model, which assumes that both additive genetic factors (A) and a unique environmental effect (E) explain the variation in susceptibility to PLE. This model estimates that the heritable component of variance in susceptibility to PLE is 84% (h<sup>2</sup> = 0.84, 95% confidence interval 0.65–0.94) and the unique environmental component (E) is 16% (E = 0.16, 95% confidence interval 0.06–0.35).

## DISCUSSION

These data provide clear evidence of a genetic basis for PLE, with an estimated heritability of 84% and 87% in the AE and ADE models, respectively. The most parsimonious fit, with the lowest AIC value, was provided by the AE model that comprises additive genetic and unique environmental components. A dominant gene effect, however, would also explain our data and could not be statistically excluded here.

The twin model provides a powerful means of examining the total genetic contribution to a given disease, especially a complex trait such as PLE. Unlike family studies, or the study of sibling pairs, potential confounders such as the variability of disease prevalence with age are removed. In addition, twins are broadly matched for cohort effects, such as exposure to sun, which might otherwise vary over time. The twin model exploits the fact that MZ twins share identical genotypes, whereas DZ twins are no more genetically alike than normal siblings. Twin modeling assumes that both types of twins share broadly the same environmental influences, which is known as the equal environment assumption (Kyvik, 1999). Although there has been some criticism of this assumption (Phillips, 1993), most studies specifically carried out to test it have supported its validity (Kyvik, 1999). Thus a higher PWC for MZ than DZ twin pairs is seen to provide evidence of the genetic contribution to any given disease trait; however, the magnitude of

the genetic effect cannot be derived from this difference because PWC is dependent on the population prevalence of the disease or trait examined. As disease prevalence in the population increases, so too does the twin concordance, irrespective of the genetic contribution (Smith, 1974). The magnitude of the genetic contribution is better quantified from twin data using model fitting, now a standard approach in twin research (Neale and Cardon, 1992).

To quantify the genetic influence on PLE in this study, we make the assumption that there is a normal underlying liability to PLE that is multifactorial, comprising both genetic and environmental components. In PLE, we know that an environmental component (sun exposure) is a prerequisite for disease expression and that the complexity of the cutaneous response to UVR would plausibly implicate the interaction of multiple genes (Norris *et al*, 1991, 1992; McFadden *et al*, 1994; Rhodes *et al*, 1995; Hadshiew *et al*, 1997; Kolgen *et al*, 1999). For a disease such as PLE with multiple genetic and environmental factors, the liability model assumes that the disease will occur when there are enough contributory factors to push the individual's liability above the threshold.

Our data indicate that both the AE and ADE models provide a parsimonious fit for PLE. Although the AE model had the lowest AIC value, it is well recognized that twin studies have little power to discriminate between additive and dominant genetic effects, especially for dichotomous traits (Neale *et al*, 1994). Thus, a dominant gene effect in addition to the additive genetic and unique environmental components described by the AE model, could also play a part in susceptibility to PLE.

The demonstration of a heritable component in PLE indicates that siblings and offspring of PLE patients will be at greater risk of developing photosensitivity than the relatives of unaffected individuals in the general population; however, at present, this is unlikely to impact on the management of PLE. We do not yet know how environmental factors interact with a susceptible genotype, whether increased or decreased sun exposure at a young age, for example, might influence the subsequent development of PLE. Clearly if behavioral or other intervention was an option for “at-risk” individuals, there could be significant public health implications for reducing morbidity and expenditure on this very common, and occasionally disabling, condition.

The ultimate goal of genetic research is to dissect the architecture of disease, both to increase understanding of the mechanisms involved and to provide novel targets for therapeutic intervention. Dizygotic twin pairs can be effectively used to delineate association and linkage, on the way to defining susceptibility genes for any given trait (Bataille, 1999; MacGregor *et al*, 2000). Patients with PLE are reported to have impaired Langerhans cell depletion following UVR exposure (Kolgen *et al*, 1999) and abnormal heat shock protein expression (McFadden *et al*, 1994). Genes involved in regulating such responses would be potential candidates to examine in PLE. They may also be relevant to other, perhaps related, autoimmune UVR-induced conditions, such as cutaneous forms of lupus erythematosus.

*We would like to thank the staff of the Twin Research Unit, as well as the twins themselves, for their help in the running of this study. Dr. T. Millard is supported by the Special Trustees of St Thomas' Hospital and Dr. H. Snieder by the British Heart Foundation. The Twin Research Unit also receives funding from the Arthritis Research Campaign, Gemini Research and the Chronic Disease Research Foundation.*

## REFERENCES

- Bataille V: The role of twin studies in the genetics of skin diseases. *Clin Exp Dermatol* 24:286–290, 1999
- Falconer DS: *Introduction to Quantitative Genetics*, 3rd edn. Harlow: Longman Scientific and Technical, 1989
- Goldsmith HH: A zygosity questionnaire for young twins: a research note. *Behav Genet* 21:257–269, 1991
- Hadshiew I, Stab F, Untiedt S, Bohnsack K, Ripcke F, Holze E: Effects of topically applied antioxidants in experimentally provoked polymorphous light eruption. *Dermatology* 195:362–368, 1997
- Jeffreys AJ, Wilson V, Thein SL: Hypervariable “minisatellite” regions in human DNA. *Nature* 314:67–73, 1985
- Kolgen W, van Weelden H, Den Hengst S, et al: CD11b+ infiltrates and persistent CD1a+ cells in UVB irradiated skin of patients with polymorphic light eruption. *Photochem Photobiol* 69:97S–97S, 1999
- Kyvik KO: Generalisability and assumptions of twin studies. In: Spector TD, Snieder H, MacGregor A (eds). *Advances in Twin and Sib-pair Analysis*. London: Greenwich Medical Media, 1999
- MacGregor AJ, Snieder H, Schork NJ, Spector TD: Twins: Novel uses to study complex traits and genetic diseases. *Trends Genet* 16:131–134, 2000
- McFadden JP, Norris PG, Cerio R, Orchard G, Hawk JL: Heat shock protein 65 immunoreactivity in experimentally induced polymorphic light eruption. *Acta Derm Venereol (Stockh)* 74:283–285, 1994
- Neale MC: *Mx: Statistical Modelling*, 4th edn. Box 126 MCV, Richmond, VA 23298: Department of Psychiatry, 1997
- Neale MC, Cardon LR: *Methodology for Genetic Studies in Twins and Families*. Dordrecht, The Netherlands: Kluwer, 1992
- Neale MC, Eaves LJ, Kendler KS: The power of the classical twin study to resolve variation in threshold traits. *Behav Genet* 24:239–258, 1994
- Norris P, Poston RN, Thomas DS, Thornhill M, Hawk J, Haskard DO: The expression of endothelial leukocyte adhesion molecule-1 (ELAM-1), intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1) in experimental cutaneous inflammation: a comparison of ultraviolet B erythema and delayed hypersensitivity. *J Invest Dermatol* 96:763–770, 1991
- Norris PG, Barker JN, Allen MH, Leiferman KM, MacDonald DM, Haskard DO, Hawk JL: Adhesion molecule expression in polymorphic light eruption. *J Invest Dermatol* 99:504–508, 1992
- Pao C, Norris PG, Corbett M, Hawk JL: Polymorphic light eruption: prevalence in Australia and England. *Br J Dermatol* 130:62–64, 1994
- Phillips DI: Twin studies in medical research: can they tell us whether diseases are genetically determined? *Lancet* 341:1008–1009, 1993
- Rhodes LE, Durham BH, Fraser WD, Friedmann PS: Dietary fish oil reduces basal and ultraviolet B-generated PGE2 levels in skin and increases the threshold to provocation of polymorphic light eruption. *J Invest Dermatol* 105:532–535, 1995
- Ros AM, Wennersten G: Current aspects of polymorphous light eruptions in Sweden. *Photodermatology* 3:298–302, 1986
- Smith C: Concordance in twins: methods and interpretation. *Am J Hum Genet* 26:454–466, 1974
- Snieder H, van Boomsma DI, Doornen LJ, De Geus EJ: Heritability of respiratory sinus arrhythmia: dependency on task and respiration rate. *Psychophysiology* 34:317–328, 1997
- StataCorp.: *Stata Statistical Software*, release 5.0. College Station, Texas: StataCorp, 1997