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Is the genetics of moliness simply the genetics of sun exposure? A path analysis of nevus counts and risk factors in British twins

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Introduction

There is ample evidence that the presence of acquired melanocytic nevi (moles) is associated with an increased risk of developing melanoma. As a result, a number of studies have been performed examining the determinants of presence and number of such nevi. Known factors associated with increased numbers are sun exposure and type of racial skin pigmentation (Green and Swerdlow, 1989). The effects of lesser differences in skin pigmentation (complexion) are less certain. In this paper, we have examined genetic and environmental determinants of nevus numbers in 45 twin pairs, and assessed the role of risk factors, particularly that of sun exposure. Specifically, we test the hypothesis that twin resemblances for nevus counts are due solely to similarities in solar exposure.

Materials and methods

The data collection of the British data set is described elsewhere (Easton et al.). Briefly, all subjects completed a questionnaire, and a single observer performed counts of all nevi greater than 3 mm diameter, grading nevi between 3-5 mm diameter on a four point "atypia" scale and the presence of lentigines on a four point scale from "none" to "excessive." Eye and hair color was recorded.

Phenotypic and genetic path analyses were performed (Heath et al., 1989), modelling discrete variables using the multiple thresholds approach with the computer programs PRELIS and LISREL (Jöreskog and Sörbom, 1989). The bivariate analysis (log total NC and sun exposure) presented used continuous variables and a maximum likelihood (ML) fit function, but the multivariate analysis used the weighted least squares (WLS) option for polychoric correlations. Because of the small sample sizes, the results of this latter analysis should be regarded with caution, although additional analyses of submodels using bootstrapped empirical covariance matrices were in agreement. We also fitted the direction-of-causation model, which uses information from the intertwin cross-trait correlations to infer temporal precedence.

There were 23 MZ and 22 same-sex DZ pairs enrolled in the study. Males comprised 53% of the subjects. Martin et al. (1978) have shown that much larger numbers of twins are needed to test more than the simplest hypotheses (e.g., genetic versus environmental determination). The failure to include male-female DZ pairs prevents testing whether the same genetic and environmental effects are acting in each sex.

Results

Phenotypic analysis. The median age of the subjects was 38 years (mean 39.0 yrs), ranging from 26 to 58. Since the majority of the twins had been born and had spent their childhood in the United Kingdom, reported exposure to sun prior to age 10 years was uniformly low (level 2 out of 7, or "average exposure in U.K."). More variation was observed between the ages of 10 and 20 years.

Preliminary phenotypic analyses were performed ignoring the genetic relatedness of the subjects. The major risk factor associated with whole body and site specific nevus counts was solar exposure between 10 and 20 years of age (Table I). Nevus counts also were associated with freckling, but not with reported skin type and hair and eye color. The 3-5 mm diameter nevus atypia score was correlated with nevus counts. Though age, sex, and zygosity were intercorrelated, they were not significantly associated with any measures of interest.

Table I. Phenotypic polychoric correlations (x 100) for sun exposure age 10-20 years (EXP) and nevus counts at five body sites

	E	H	T	A	L	B
EXP	--					
Head	-5	--				
Trunk	33	36	--			
Arms	28	33	54	--		
Legs	25	31	52	55	--	
Back	49	37	55	48	34	--

Nevus counts for twins with "average U.K. sun exposure" or lower (levels 1-2 out of 7) at age 10-20 years were 4.2, compared to 8.5 for the high exposure group (for log transformed scores, $t = 3.7$, $p = 0.004$). Similar analysis for solar exposure after age 20 found no such effect. There was no correlation between numbers of nevi over 5 mm diameter and solar exposure, probably because of the small numbers in the samples.

As a result we have focused on sun exposure between ages 10 and 20 years (EXP) as the only important covariate of nevus count in further analysis.

Univariate genetic analysis. For this and later analysis, we have combined the "shirt" areas (trunk and back) into one "torso" area. MZ twins were more concordant than DZ twins on total and site specific nevus counts and sun exposure, implying a genetic component to variation in these traits (Table II).

Path models were then fitted to the observed correlations. Because of the small sample size, these univariate analyses had low power to discriminate between modes of transmission. For solar exposure, the genetic model gave a better fit than the shared environment model, though the latter could not be rejected (shared environment model $X_1^2 = 3.21$, $p = 0.07$). This suggests that exposure might explain MZ-DZ twin differences in nevus count.

Multivariate genetic analysis. Since solar exposure was strongly associated with total nevus count, we first fitted bivariate models to (untransformed) EXP and log transformed total number of nevi between 3 and 5 mm diameter (Table III). Both genetic common factor models, and direction of causation models were fitted (Table IV).

The initial common factor model fitted well, a common nonadditive genetic factor fitting slightly better than a common additive factor. These factors could not be estimated simultaneously, reflecting the small sample size and the large difference between the MZ and DZ correlations for these traits. The equivalent reciprocal causation model fitted well (Model 1), and the Nevi → EXP path could be discarded (Models 3 vs. 1). The preferred model (Fig. 1) was comprised of nonadditive genetic factors controlling sun exposure (Models 5 vs. 2) and nevus count separately (Models 6 vs. 2), twin-specific environmental factors for both, and a phenotypic path running from sun exposure to nevus count (Models 4 vs. 2). Genes directly explained 65% of the variance of nevus count, and sun exposure a further 15%, of which 12% was indirectly genetic from the genes influencing EXP.

We then considered a more elaborate model examining polychoric correlations between EXP and nevus count at four body sites. We allowed the effect of EXP and genes to differ at each body site (Fig. 2). The likelihood ratio comparisons of models (Table V) were consistent with the earlier bivariate models in that genetic factors for both sun exposure and nevus counts were confirmed. Genetic factors specific to body sites were rejected, as were individual or familial environmental effects common to all body sites (other than EXP). The path coefficients from EXP and the nevus genetic factor to each site could not be constrained to be equal, indicating differential importance of sun exposure, genetic factors, and other factors at each body site. The pattern of coefficient values was consistent with previous genetic studies of skin reflectance (Clark et al., 1981).

Discussion

We are aware of only one previous study of cutaneous nevi in twins (Siemens, 1924). Siemens concluded that total nevus count was under some degree of genetic control. The present study confirms that solar exposure prior to age 20, but not later, is a major determinant of nevus numbers. Solar exposure was more strongly correlated among MZ twins than DZ twins, and partially explained the genetic correlations between twins for nevus count. After allowing for these similarities in exposure, a remaining genetic influence controlling nevus count was detected. It is interesting to notice how the patterns of the genetic loadings varied at each anatomical site, reflecting the relative importance of exposure as modulated by clothing, and genes, the latter being more significant on well covered sites such as the trunk, as would be expected. The large differences between the MZ and DZ correlation for nevus count and sun exposure may reflect sampling problems, but suggest epistasis (Eaves, 1988), although the small sample size does not allow this

Table II. Twin polychoric correlations (x 100) for nevus counts at four body sites and sun exposure between 10 and 20 years of age

						Dizygotic twins (22 pairs)				
	E1	H1	T1	A1	L1	E2	H2	T2	A2	L2
EXP1	--	89	92	-04	-96	**35**	07	11	-29	-31
Head1	-51	--	63	06	-39	07	**06**	-22	-26	-34
Tors1	61	10	--	32	-28	19	15	**14**	-23	14
Arms1	27	45	56	--	25	-07	-20	-24	**-19**	-11
Legs1	00	43	29	50	--	-27	-12	-05	-07	**37**
EXP2	**96**	-28	66	41	-17	--	38	13	37	61
Head2	-16	**48**	38	29	46	-13	--	56	43	46
Tors2	34	56	**75**	75	58	44	43	--	72	36
Arms2	28	20	39	**62**	25	41	12	63	--	51
Legs2	53	-15	57	45	**51**	38	20	53	27	--

Monozygotic twins (23 pairs)

Table III. Pearsonian correlations (x 100) for log total nevus count (3-5 mm) and sun exposure ages 10-20 years

			Dizygotic twins (22 pairs)	
	EXP1	LNC1	EXP2	LNC2
EXP1	--	43	**22**	-03
LNC1	41	--	-08	**-17**
EXP2	**86**	48	--	30
LNC2	41	**78**	47	--

Monozygotic twins (23 pairs)

Table IV. Bivariate direction of causation models for log transformed total nevus count (3-5 mm) and sun exposure age 10-20 years. D_{exp} and D_{nev} are nonadditive genetic factors specific to sun exposure and nevus count. C_{nev} is a shared environmental factor for nevus count.

Model		X^2	df	AIC
Common genes model		4.0	7	-10.1
1. Reciprocal model		4.0	7	-10.0
2. EXP→Nevi		**6.7**	**8**	**-9.3**
3. Nevi→EXP		8.6	8	-7.4
4. No EXP-Nevi correlation		16.5	9	-1.5
5. EXP→Nevi, No D_{nev}		19.9	9	1.9
6. EXP→Nevi, No D_{exp}		36.6	10	16.6
7. EXP→Nevi, C_{nev}		16.1	8	0.1
Hierarchical comparisons		LR X^2	df	P
Reciprocal pathway	base model			
EXP→**Nevi**	2 v. 1	2.7	1	0.10
Nevi→EXP	3 v. 1	4.6	1	0.03
Sun exposure not a significance covariate	4 v.2	9.8	1	0.00
No genes for Expo	5 v. 2	30.0	1	0.00
No genes for Nevi	6 v. 2	13.2	1	0.00

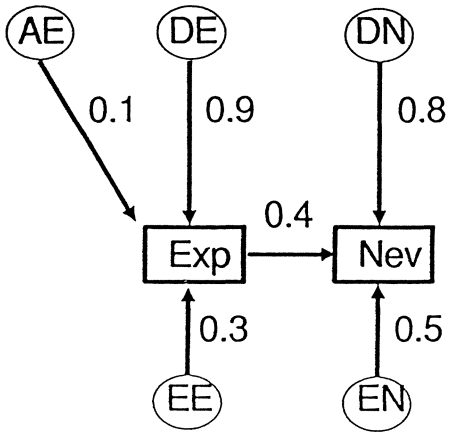

Fig. 1. Path diagram of preferred model for total nevus count and teenage sun exposure. (AE = additive genetic, DE = nonadditive genetic and EE = unshared environmental components for sun exposure; DN, EN = nonadditive genetic, unshared environment for nevus count).

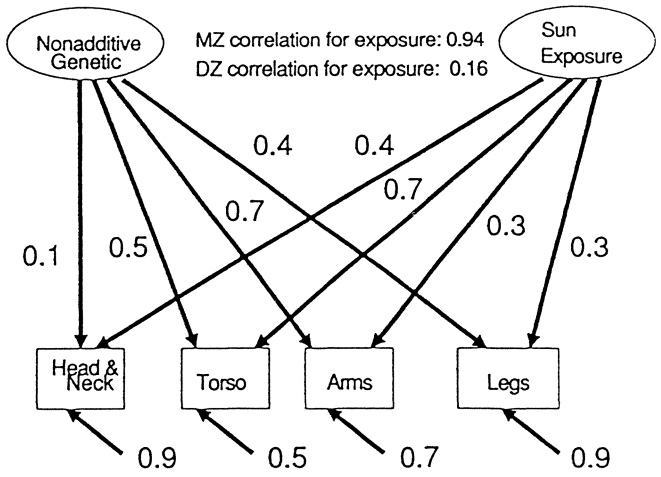

Fig. 2. Path diagram for preferred model for teenage sun exposure and nevus count at four body sites.

Table V. Testing of independent pathways multivariate genetic models for solar exposure and nevus counts at four body sites

Model	X^2	df	AIC
1. Exposure; Comm A, C and E; Specific E	128.8	64	0.8
2. Exposure; Comm A; Specific E	**133.4**	**72**	**-10.6**
3. Exposure; Specific E	151.3	76	-0.7
4. Common A; Specific E	347.6	76	195.6
5. Exposure; Common A; Specific A and E	131.1	68	-4.9
6. Model 2 but Exposure $r_{MZ} = r_{DZ}$	178.2	77	4.2

Hierarchical comparisons		LR X^2	df	P
No common ind. or shared environ.	2 v. 1	4.6	8	0.80
No common genetic factor	3 v. 2	17.9	4	0.00
Exposure not a significant covariate	4 v. 2	214.2	4	0.00
No site-specific genes	2 v. 5	2.3	4	0.68
No genetic component for exposure	6 v. 2	39.2	1	0.00

to be confirmed. Finally, teenage sun exposure in this British sample would be partially determined by level of interest in outdoor sports. This would reflect sporting ability (size or agility), which must have a large genetic component, and so might explain the increased concordance in MZ twins for sun exposure. It should be noted that there were no mean differences between the MZ and DZ twin groups in sun exposure at this age.

In conclusion, we have found that nevus counts and sun exposure both exhibit evidence of being under genetic control, and that sun exposure was a large determinant of nevus count. A problem underlying our analysis is the small sample size. Another problem is that the number of nevi over 5 mm diameter, one of the better predictors of risk of melanoma, was small, and so no definite trends were detected. A larger study, including more subjects with larger nevi, perhaps based in a location with higher and more varied sun exposure, would better examine this important subset of atypical nevi, and allow confirmation of the present findings.

Acknowledgements

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References

Clark P, Stark AE, Walsh RJ, Jardine R, Martin NG: A twin study of skin reflectance. Ann Human Biol 8:529-541 (1981).

Eaves LJ: Dominance alone is not enough. Behav Genet 18:27-33 (1988).

Green A, Swerdlow AJ: Epidemiology of melanocytic nevi. Epidemiol Rev 11:204-221 (1989).

Heath AC, Neale MC, Hewitt JK, Eaves LJ, Fulker DW: Testing structural equation models for twin data using LISREL. Behav Genet 19:9-35 (1989).

Jöreskog KG, Sörbom D: LISREL 7. A Guide to the Program and Applications (SPSS Inc, Chicago, 1989).

Martin NG, Eaves LJ, Kearsey MJ, Davies P: The power of the classical twin study. Heredity 40:97-116 (1978).

Siemens HW: Der Zwillingspathologie (Springer, Berlin, 1924).