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Heritability of naevus patterns in an adult twin cohort from the Brisbane Twin Registry: a cross-sectional study

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Conflicts of interest
None declared.

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Summary

Background Heritability of naevi counts is widely acknowledged as a potential surveillance parameter for prevention purposes. The contribution of heritability to the changes seen in naevus number and morphology over time and their corresponding dermoscopic characteristics is unknown, but is important to understand in order to account for adequate prevention measures.

Objectives To identify naevus characteristics that are strongly influenced by heritability.

Methods This cross-sectional study included 220 individuals [76 monozygotic (MZ), 144 dizygotic (DZ)], recruited from the Brisbane Twin Naevus Study. Participants received full body imaging and dermoscopy of naevi ≥ 5 mm in diameter. Dermoscopic type, total naevus count (TNC), change in TNC with age, and naevus distribution, size, colour and profile were compared between MZ and DZ twins. Heritability of these traits was assessed via Falconer's estimate.

Results Significant differences were found in comparing MZ and DZ twins for TNC, numbers of naevi 5·0–7·9 mm in diameter, counts of light-brown naevi, naevi on the back and sun-protected sites, and naevi with the 'nonspecific' dermoscopic pattern.

Conclusions This study strongly supports a heritable component to TNC, as well as changes in TNC, and the number of medium-sized naevi, light-brown naevi, specific sites and certain dermoscopic features in adults. These characteristics should be taken into account by naevus surveillance programmes and further studied to identify candidate gene associations for clinical and dermoscopic patterns in conjunction with melanoma risk stratification.

What's already known about this topic?

- Total naevus counts and distributions on body sites are presumably heritable, but the inheritable associations for time-dependent changes are unclear.
- Dermoscopic naevus pattern differs with age and body site but its heritability is uncertain.

What does this study add?

- Total naevus counts and time-dependent changes in total naevus counts are heritable.
- Studying the heritability of dermoscopic naevus patterns provides a platform for examination of candidate genes regulating clinical and dermoscopic naevus patterns.

Naevi are known precursors for melanoma,[1,2] and a high total naevus count (TNC) is a strong risk factor for melanoma in white people.[3] Thus, understanding naevogenesis, the heritability of clinical and dermoscopic naevus patterns, and their links to melanoma development are important for improving early detection of melanoma.

Compared with conventional histopathology, clinical examination and dermoscopy are useful noninvasive tools for melanoma diagnosis and allow for ongoing monitoring.[4] Among both experienced examiners and laypersons, dermoscopy has a higher accuracy for melanoma diagnosis compared with visual inspection alone.[4–6] Twin studies comparing phenotypes of monozygotic (MZ) or dizygotic (DZ) twins are one approach in evaluating the broad genetic and environmental contributions to a trait, in this case clinical and dermoscopic naevus patterns.[7] A greater similarity between MZ pairs than DZ pairs can then be attributed to genetic factors, whereas a comparable degree of similarity in MZ and DZ twins suggests an environmental influence.[7] Clinical naevus patterns of twins have been examined in adolescent teenagers and adult twins of European ancestry within Queensland, Australia, and the U.K., but not for the same person as an adolescent then as an adult. Previous studies found a high heritability of TNC and naevus distribution for sun-exposed sites.[8–10] Zhu *et al.* described heritability of 68% for TNC in a study of 352 Australian 12-year-old twin pairs.[8] Wachsmuth *et al.* found a similar heritability of 65% for TNC in a study of 221 U.K. twin pairs aged 10–18 years.[9] Bataille *et al.* reported a heritability of 62% for naevus distribution at sun-exposed sites in an adult female U.K. twin population.[10] In a study of 12-year-old Australian twins by McGregor *et al.*,[11] a wide variance of 40–80% in naevus size and colour was attributed to genetics.[11] For naevus profile, heritability was 69% for raised naevi and 42% for flat naevi.[8,12]

Dermoscopic naevus patterns differ with age and body site; the globular type is more common in those younger than 15 years of age and the reticular type more common in those older than 15 years, but the heritability of dermoscopic naevus patterns is not known.[1,13–15] Dermoscopic naevus patterns do not differ significantly according to melanoma risk per age and body site.[1] Based on this existing information, it has been theorized that dermoscopic naevus patterns are at least partly heritable.[14]

This study aims to investigate whether heritability influences clinical naevus count and dermoscopic naevus patterns. It is the first study to examine and describe heritability of dermoscopic naevus patterns in twins. Further, TNC were compared in adult twins to previous TNCs during adolescence of the same individuals. We found significant differences between MZ and DZ twins for a number of clinical parameters, for example TNCs or number of naevi on sun-protected sites and the 'nonspecific' dermoscopic pattern. Based on our findings of time-dependent changes of naevi in twins bound to high heritability, more in-depth investigations into the genetic profile of particular types of naevi are warranted.

Patients and methods

Study population

In total, 220 twins (110 pairs: 14 MZ male pairs; 24 DZ male pairs; 24 MZ female pairs; 31 DZ female pairs; 17 male/female DZ pairs), aged 26–32 years, of European ancestry were recruited from previous participants of the Brisbane Twin Naevus Study (BTNS) through the QIMR Berghofer Medical Research Institute from 10 April 2012 to 15 January 2013. The zygosity of twins was determined from the existing BTNS database. Volunteers were recruited by posting letters to previous participants of the BTNS. Participants were all long-term residents of Queensland and already had baseline clinical total naevus counts recorded at 12 and 14 years of age.

Data collection

All study participants had digital images of 16 body sites and individual dermoscopic images of significant naevi recorded with sequential total body photography and dermoscopy (FotoFinder Systems GmbH, Bad Birnbach, Germany). Significant naevi were classified as those measuring ≥ 5 mm at body sites excluding scalp, buttocks, mucosal surfaces and genitalia in both sexes and breasts in women. Predominant dermoscopic types (globular, reticular, nonspecific and other), defined as at least one-third of the surface area of the naevus,[16] were recorded for significant naevi, as well as naevus colour (light brown, mid-brown, dark brown or pink) and naevus profile (flat, dome-shaped, plaque or papillomatous). Naevi were recorded using the FotoFinder Systems program calibration function. From this information, total naevus count, naevus count on sun-protected sites (back and chest/abdomen) and on sun-exposed sites (head/neck, upper limbs and lower limbs), and counts for size categories (≥ 5·0–7·9 mm, ≥ 8 mm) were calculated. Raw data on naevi recorded in total, on body sites and according to dermoscopic types are presented in Tables S1–S3 (see Supporting Information). The change in naevus count from 12–14 years of age to 26–32 years of age was determined.

Statistical analysis

Twin pairs were randomly assigned as twin 1 and 2. Using the R statistics program (https://www.r-project.org), appropriate transformations for each parameter were obtained. Spearman's rank correlations with bootstrap technique and 1000 repetitions for two-tailed 95% confidence intervals (CIs) were obtained for each parameter for MZ and DZ twins and the difference between MZ and DZ twins. Heritability was calculated by using the Falconer's estimate, by doubling the difference in correlation between MZ and DZ twins. Bootstrapping was chosen to give robust 95% CIs for this measure in the present study because of the relatively small sample size. The derivation is as follows: $MZr = (Vg + Vd + Vc)/Vp$; $DZr = (0{\cdot}5\ Vg + 0{\cdot}25\ Vd + Vc)/Vp$;

$2*(MZr - DZr) = (Vg + 1{\cdot}5\ Vd)/Vp$, where Vg is the additive genetic variance, Vd the biometrical dominance variance, Vc, the variance due to shared family environment and Vp the total phenotypic variance of the trait. Vc and Vd are completely confounded in the classical twin design, so only one of these variances can be estimated for given MZ and DZ twin correlations. The broad heritability is defined as $Hb = (Vg + Vd)/Vp$ so the Falconer estimator gives $Hb + (0{\cdot}5 * Vd)/Vp$.[17]

The overall smoothed regression line for changes in TNC in nontwin controls was estimated via localized regression (also known as loess or LOWESS regression).[18,19] This procedure was carried out using the R locfit package (version 1.5). The age regression line for the twins is the average of the individual slopes across occasions.

Ethics

Ethical approval was granted by the University of Queensland (UQ) School of Medicine Low Risk Ethical Review Committee (clearance no. 2012-SOMILRE-0021, 2009001590 and amendment 03/10/2011), Princess Alexandra Hospital Human Research Ethics Committee (clearance no. HREC/09/QPAH/162 and amendment 18/08/2011) and the QIMR Ethics Committee (BNMS/P193).

Results

Changes in total naevus count

As adults, intraclass correlations (ICC) for TNC $\geq$ 5 mm was higher in MZ twins (0·84) than in DZ twins (0·37) ($P < 0{\cdot}01$) (Fig. 1a; Table 1), with a heritability of 100% (95% CI 12–100). ICC for changes in TNC $\geq$ 5 mm between the age of 12–14 years and 26–34 years was higher in MZ twins (0·90) than in DZ twins (0·35) – a highly significant difference ($P < 0{\cdot}01$), with a heritability of 100% (95% CI 16–100). There was an increase in TNC between younger ages and adults, manifested by the increase of the average regression line, which is in concordance with a control population showing a steady increase to the age of 50 years (Fig. 1b).

Naevus distribution and size

ICCs for MZ twins (rMZ) was higher than for DZ twins (rDZ) for naevi count on the chest/abdomen ($rMZ = 0{\cdot}52$ and $rDZ = -0{\cdot}04$; Fig. 2a), upper limbs ($rMZ = 0{\cdot}67$ and $rDZ = 0{\cdot}18$; Fig. 2b) and lower limbs ($rMZ = 0{\cdot}71$ and $rDZ = 0{\cdot}39$; Fig. 2c) (Table 1). No significant difference was found in ICCs between MZ and DZ twins for head/neck and back. Correlations for combined sun-exposed sites were significantly higher in MZ twins (0·75) than in DZ twins (0·22) ($P = 0{\cdot}01$), with a heritability of 100% (95% CI 16–100; Fig. 2d). Correlations for combined sun-protected sites were not significantly higher in MZ twins (0·63) than in DZ twins (0·25) ($P = 0{\cdot}08$), with a heritability of 78% (95% CI 0–100). ICCs were significantly higher for counts of naevi 5·0–7·9 mm in diameter ($P = 0{\cdot}03$; Fig. 3a) in MZ twins (0·85) compared with DZ twins (0·47), with a heritability of 76% (95% CI 2–100).

Naevus colours and profile

ICCs were higher in MZ twins (0·77) than in DZ twins (0·33) for the count of light-brown naevi [$P = 0{\cdot}01$; heritability of 88% (95% CI 0–100)] (Fig. 3b, Table 1). No significant differences were found for medium-brown, dark-brown or pink naevi. There was no significant difference in ICC between MZ and DZ for all naevus profiles.

Dermoscopic type

ICCs were higher for MZ twins (0·78) than for DZ twins (0·48) for nonspecific naevi count ($P = 0{\cdot}03$), with a heritability of 60% (95% CI 0–100; Fig. 3c, Table 1). No significant difference was found for globular naevi ($P = 0{\cdot}14$) or reticular naevi ($P = 0{\cdot}48$) count.

Discussion

In the present study, we compared clinical characteristics and dermoscopic features of naevi in adult MZ and DZ twins from the BTNS, based on the assumption that a high heritability of most clinical and dermoscopic naevus patterns is expected. As observed 10 years ago, when our twin study participants were adolescents, there was a significant difference in TNCs between MZ and DZ twins as adults. Heritability of TNC was high for twins aged 26–32 years, being the same as the identical population of twins aged 12–14 years. Interestingly, heritability of TNC for DZ from which twins for this study were recruited was lower (68%), with shared family environment and individual environment accounting for 26% and 6% of variance, respectively.[7] The higher heritability found in this adult population may be attributed to the lower power, where the shared family environment (close to 0% for adults) tends to inflate the heritability estimate.

There were significant differences between MZ and DZ twins for change in TNC with a high heritability from adolescence to adulthood. This supports the findings of Bataille *et al.* on TNC in twin populations of varying ages, for which a variance of 84% was found in TNC attributed to additive genetic factors for patients > 45 years of age and 36% for patients < 45 years of age.[10] Thus, heritability of TNC appears to remain high or increases with older age, indicating a genetic influence. In our study population, TNC increased between the ages of 12–14 years and 26–32 years. Similarly, a U.K. study found that TNC peaked around 25–30 years of age and then decreased from middle-age onwards.[20] Duffy *et al.* demonstrated that every copy of the *IRF4* single nucleotide polymorphism rs 12203592*T allele increases TNC 30 times in Australian adolescents compared with five times in British adolescents.[21] TNC was counted by naked eye by investigators

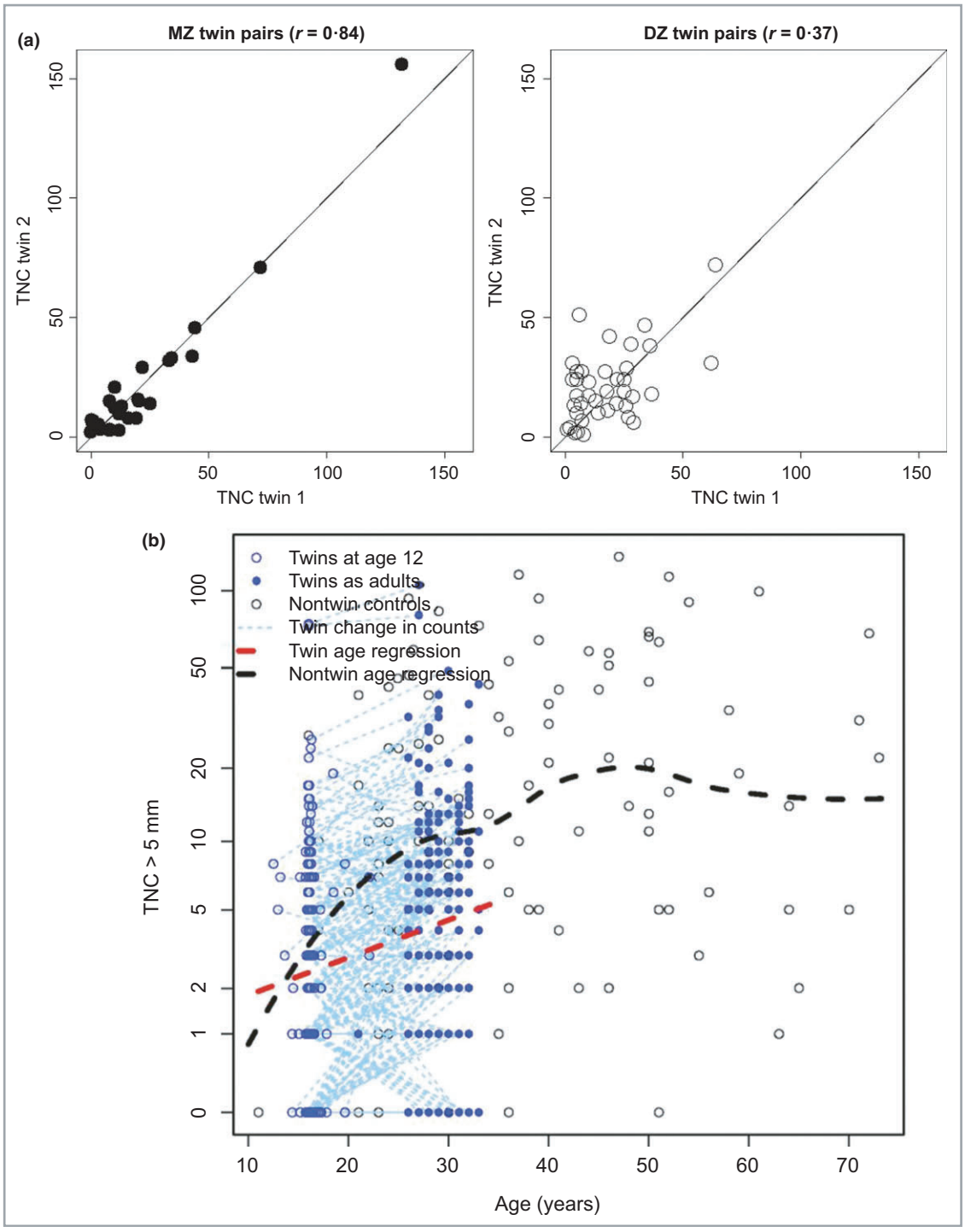

Fig. 1. Correlation and change of total naevus count (TNC) in adult and young twins. (a) Correlations for TNC for twin 1 against twin 2 as adults, according to zygosity. (b) Change in TNC over 12–14 and 26–34 years of age for 220 individual twins. Line of best fit for change in TNC shown as a red dashed line. Nontwin controls show the same steady increase in naevi numbers up to the age of 50 years (black dashed line). MZ, monozygous; DZ, dizygous.

14–20 years ago, whereas this study used a combination of naked eye and Fotofinder technology. Therefore, the finding that change in naevus count is genetically determined is relevant, particularly in terms of ongoing monitoring of melanocytic naevi for the individual and family members.

For sun-exposed sites, ICCs were higher in MZ than DZ twins, with a high heritability. For sun-protected sites, ICCs were higher in MZ than DZ twins, but with lower heritability. This does not align with our initial prediction of a greater genetic influence for sun-protected sites. Alternatively, the

Table 1 Intraclass correlations, difference in correlation, P-value and heritability in 27 monozygotic (MZ) and 39 dizygotic (DZ) twins for naevi ≥ 5 mm

	Intraclass Spearman rank correlation coefficient r (95% CI)				
	MZ	DZ	Difference(95% CI)	P-value	Percentage heritability (95% CI)
Present TNC ≥ 5 mm	0·84 (0·74–1·00)	0·37 (0·12–0·67)	0·48 (0·16–0·79)	< 0·01	100 (12–100)
TNC at 14 years of age	0·90 (0·80–1·00)	0·18 (0·00–0·57)	0·72 (0·31–1·00)	< 0·01	100 (62–100)
TNC at 12 years of age	0·92 (0·81–1·00)	0·39 (0·05–0·77)	0·52 (0·16–0·91)	0·01	100 (32–100)
Change in TNC with age ≥ 5 mm	0·90 (0·80–1·00)	0·35 (0·06–0·66)	0·55 (0·23–0·88)	< 0·01	100 (16–100)
Naevus distribution					
Head/neck	0·37 (0·00–0·82)	0·18 (0·00–0·57)	0·18 (−0·44 to 0·83)	0·26	36 (0–100)
Back	0·44 (0·04–0·88)	0·38 (0·00–0·80)	0·06 (−0·51 to 0·66)	0·42	12 (0–100)
Chest/abdomen	0·52 (0·09–0·97)	−0·04 (0·00–0·37)	0·57 (−0·06 to 1·00)	0·03	100 (0–100)
Upper limbs	0·67 (0·37–1·00)	0·18 (0·00–0·59)	0·49 (−0·01 to 1·00)	0·02	98 (0–100)
Lower limbs	0·71 (0·44–1·00)	0·39 (0·04–0·77)	0·32 (−0·14 to 0·79)	0·04	64 (0–100)
Sun-exposed sites	0·75 (0·49–1·00)	0·22 (0·00–0·61)	0·53 (0·08–1·00)	0·01	100 (16–100)
Sun-protected sites	0·63 (0·32–1·00)	0·25 (0·00–0·67)	0·39 (−0·15 to 0·92)	0·08	78 (0–100)
Naevus size (mm)					
5·0–7·9	0·85 (0·71–1·00)	0·47 (0·14–0·82)	0·38 (0·01–0·76)	0·03	76 (2–100)
≥ 8	0·45 (0·00–0·91)	−0·05 (0·00–0·33)	0·50 (−0·09 to 1·00)	0·05	100 (0–100)
Naevus colour					
Light brown	0·77 (0·51–1·00)	0·33 (0·00–0·73)	0·44 (−0·01 to 0·92)	0·01	88 (0–100)
Medium brown	0·49 (0·09–0·93)	0·27 (0·00–0·70)	0·22 (−0·39 to 0·85)	0·16	44 (0–100)
Dark brown[b]	0·21 (0·00–0·70)	0·51 (0·21–0·84)	−0·30 (−0·86 to 0·31)	0·87	−60 (−100 to 62)[a]
Pink	0·59 (0·15–1·00)	0·26 (0·00–0·66)	0·33 (−0·25 to 0·93)	0·14	66 (0–100)
Naevus profile					
Flat	0·68 (0·34–1·00)	0·51 (0·16–0·89)	0·18 (−0·33 to 0·67)	0·19	36 (0–100)
Plaque	0·49 (0·19–0·83)	0·17 (0·00–0·55)	0·32 (−0·17 to 0·83)	0·11	64 (0–100)
Dome-shaped[c]	0·17 (0·00–0·61)	0·41 (0·04–0·80)	−0·24 (−0·85 to 0·33)	0·80	−48 (−100 to 66)[a]
Papillomatous	0·38 (0·00–0·81)	0·30 (0·00–0·69)	0·08 (−0·48 to 0·65)	0·42	16 (0–100)
Dermoscopic type					
Globular	0·41 (0·02–0·84)	0·08 (0·00–0·48)	0·33 (−0·23 to 0·91)	0·14	66 (0–100)
Reticular	0·35 (0·00–0·83)	0·32 (0·00–0·72)	0·03 (−0·58 to 0·66)	0·48	6 (0–100)
Nonspecific	0·78 (0·55–1·00)	0·48 (0·18–0·83)	0·30 (−0·11 to 0·73)	0·03	60 (0–100)

CI, confidence interval; TNC, total naevus count. [a]Small numbers; [b]median 0, interquartile range 0–1; [c]median 0, interquartile range 0–2.

genetic effect on naevus induction may be imprinted upon ultraviolet (UV) irradiation in areas of chronic sun exposure. Nevertheless, the CIs were wide for sun-protected sites (−30% to 100%). Using an automated power analysis by Visscher to achieve a power of 0·80 and in order to detect a true additive genetic variance of 78%, the optimum sample size would be 45 twin pairs (26 MZ and 19 DZ twins).[22,23] It appears that the size of this study was sufficient but had different MZ proportions. Hence, it is possible that the sun-protected sites may actually be genetically influenced as the P-value is close to 0·05. It would be interesting for future studies with appropriate MZ to DZ ratios to investigate this hypothesis. Breakdown of counts per body site also yielded interesting results. There was a significant difference between MZ and DZ twins for naevi count on the chest/abdomen, with high heritability. The difference between MZ and DZ twins was not significant for the head/neck, with a low heritability. These results for the chest/abdomen (sun-protected sites) and head/neck (sun-exposed sites) support the results of a U.K. twin study of patients aged 18–72 years.[10] However, there were also significant differences between MZ and DZ twins for the upper limbs (heritability of 98%) and lower limbs (heritability of 64%), which are sun-exposed body sites. The difference between MZ and DZ twins was not significant for the back, a sun-protected site, with a very low heritability. This corroborates the higher heritability for sun-exposed sites compared with sun-protected sites found for 12-year-old twins from the U.K.[9] Wachsmuth *et al.* (2001) proposed that naevi on sun-exposed sites may have a threshold of UV radiation for genetic expression.[9] Therefore, another hypothesis is that the upper limbs, lower limbs and back have a higher UV radiation threshold for genetic expression of naevi, while naevi on the head/neck and chest have a direct dose-dependent response to UV radiation. Again, these results imply that further studies are needed.

There was a significant difference between MZ and DZ twins for counts of naevi 5·0–7·9 mm in diameter, with a heritability of 76%. Hence, the differences between individuals for counts of naevi < 8 mm in diameter appear to be predominantly influenced by genetics. These heritabilities were higher than the findings of McGregor *et al.* for Australian 12-year-old twins,[11] where 40–80% of variance in naevus size and colour

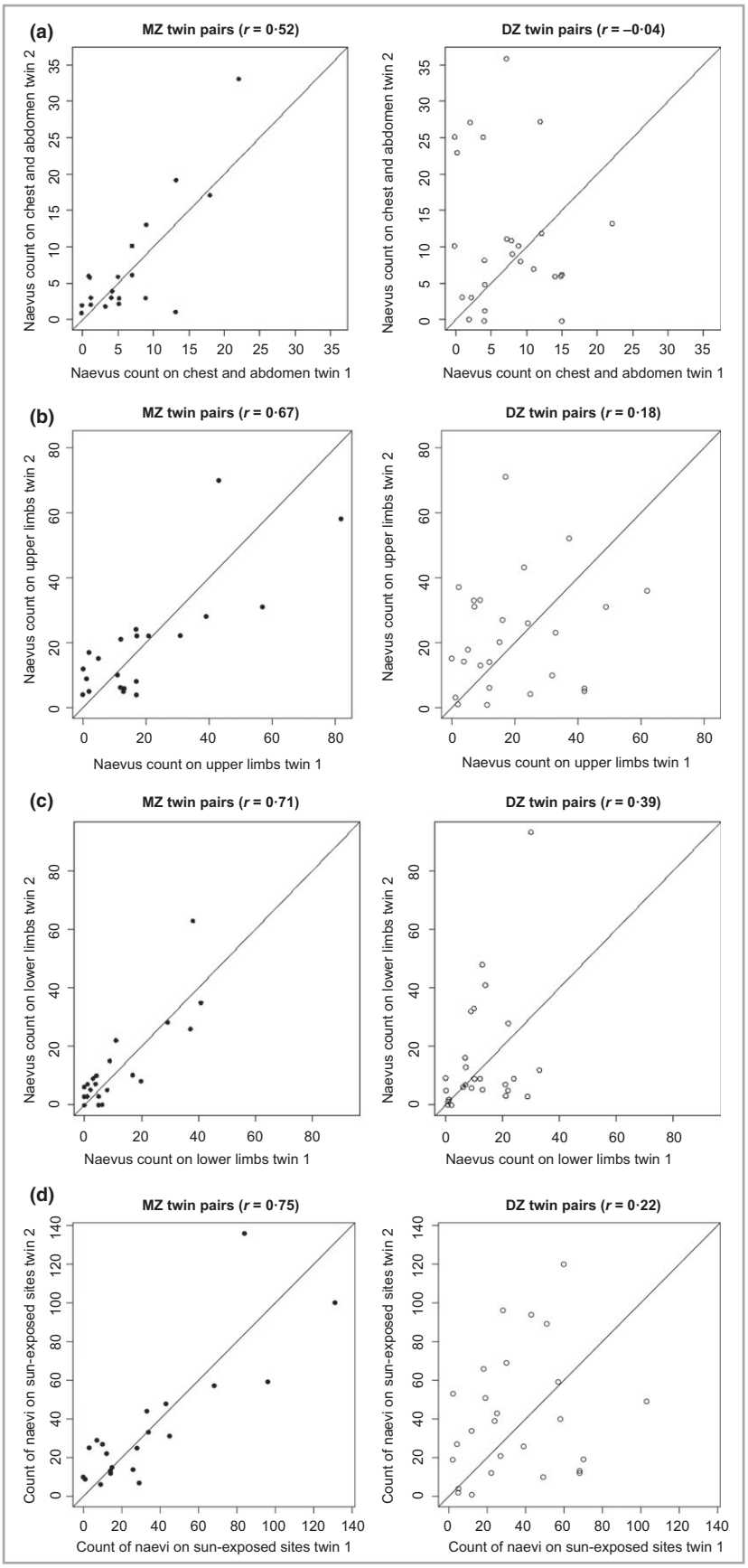

Fig 2. Correlation for count of naevi on different body sites for twin 1 vs. twin 2, according to zygosity. (a) Count of naevi on chest and abdomen for twin 1 vs. twin 2. (b) Number of naevi on upper limbs for twin 1 vs. twin 2. (c) Naevi on lower limbs for twin 1 vs. twin 2. (d) Count of naevi on sun-exposed sites for twin 1 vs. twin 2. MZ, monozygous; DZ, dizygous.

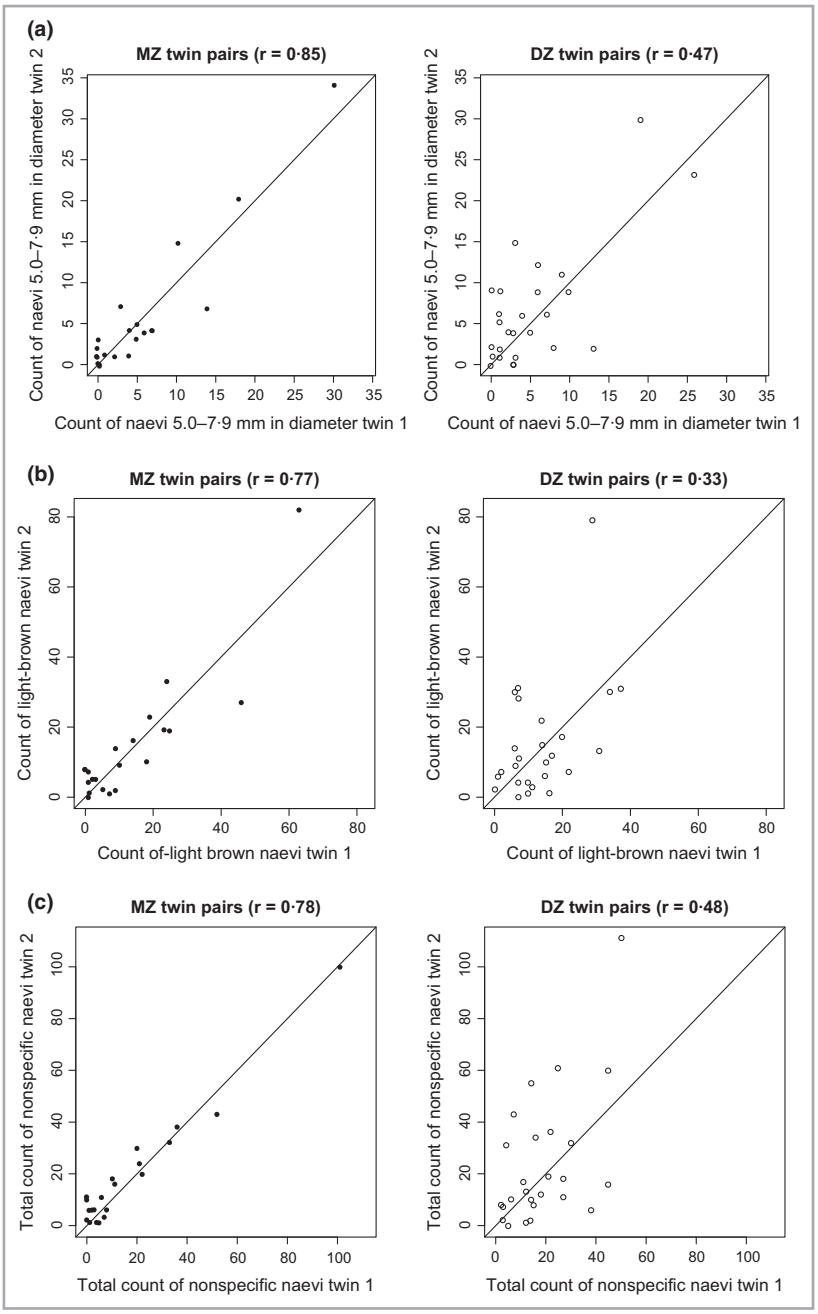

Fig 3. Correlation for count of naevi characteristics for twin 1 vs. twin 2 according to zygosity. (a) Count of naevi 5·0–7·9 mm in diameter for twin 1 vs. twin 2. (b) Numbers of light-brown naevi for twin 1 vs. twin 2. (c) Count of naevi with a nonspecific dermoscopic pattern for twin 1 vs. twin 2. MZ, monozygous; DZ, dizygous.

were attributed to genetic factors. There was no significant difference between MZ and DZ twins for naevi > 8 mm in diameter, suggesting that formation of the largest naevi is mainly influenced by environmental factors. The wide CIs for heritabilities of naevi 5·0–7·9 mm in diameter (2–100%) suggest that a larger sample size may be needed to achieve a strong power of 0·80 and more robust results for future studies.[22,23]

Dermoscopy might act as a guide in determining specific patterns attributed to heritability. The nonspecific pattern showed a significant difference between MZ and DZ twins, with a heritability of 60% but with wide CIs. Piliouras *et al.* found that the structureless/nonspecific type persisted into older ages, whereas reticular and globular types disappeared;[15] therefore, the nonspecific type seems to be present at all ages, tentatively suggesting that genetics may play a role in the formation of nonspecific naevi. There was no significant difference between MZ and DZ twins for globular and reticular naevi. Therefore, it seems that these types may be influenced by the environment. In particular, the reticular type had very low heritability of 6% but with a wide CI. This is consistent with a study by Zalaudek *et al.*,[24] which found via the ultra-deep pyrosequencing method that 100% of globular naevi and 75% of reticular naevi were *BRAF* V600E-positive.[24] The dual theory of naevogenesis of Zalaudek *et al.* proposed that the globular pattern is more consistent with the endogenous pathway influenced by genetics, as the globular pattern predominates in 0–15-year-olds.[14] Interestingly, the heritability

for the globular type was higher than for the nonspecific type. However, the wide CIs suggest that further investigation with a larger sample size could clarify the amount of genetic and environmental influence on dermoscopic patterns. To achieve a power of 0·80 to detect genetic effects for globular and nonspecific types, 97 twin pairs (53 MZ, 44 DZ) and 139 twin pairs (75 MZ, 64 DZ) would be needed, respectively.[22,23]

The main limitation of this study was the sample size and wide CIs for some parameters. The data were not normally distributed, so Spearman's rank correlation, a robust nonparametric alternative to Pearson's correlation, was used. Statistically significant P-values were obtained, corroborating previous data for all clinical naevus counts and dermoscopic types. Findings from this study have also yielded useful considerations for further studies. In order to detect significant interstudy differences for naevus profile, size and dermoscopic type, the study population would have to be at least doubled. Quantitative measurements of colour could be used in future studies as a more precise method. Ideally, all naevi $\geq$ 2 mm in size would be imaged dermoscopically and assessed for colour, profile and dermoscopic type; however, owing to the intensive manual labour involved, stringent criteria were used as per the methods. Despite this, using the same method for all twin pairs to reduce confounding factors minimized the impact of this limitation on the results. The findings would only be generalizable to the Queensland population and those with European ancestry as per the sample population. The high heritability of change in TNC with age strongly suggests the existence of candidate genes involved in naevogenesis and naevus evolution, possibly induced by UV radiation. Contrary to predictions, the heritability of naevus counts per body site was higher for sun-exposed sites, suggesting that genetic effects may be more noticeable with strong UV radiation exposure.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Table S1. Raw number of naevi counts for total and dermoscopic pattern.

Table S2. Raw number of naevi counts per body site and dermoscopic pattern.

Table S3. Numbers of naevi for different dermoscopic patterns on body site.