Body site-specific genetic effects influence naevus count distribution in women

Alessia Visconti¹, Simone Ribero², Marianna Sanna¹, Timothy D. Spector¹, Veronique Bataille¹,³,* and Mario Falchi¹,*

¹Department of Twin Research & Genetic Epidemiology, King’s College London, London, UK
²Department of Medical Sciences, Section of Dermatology, University of Turin, Turin, Italy
³Department of Dermatology, West Herts NHS Trust, Herts, UK

*V. Bataille and M. Falchi share senior authorship

Abstract

Body site is highly relevant for melanoma: it affects prognosis and varies according to the patient’s sex. The distribution of naevi, a major risk factor for melanoma, at different body sites also varies according to sex in childhood. Using naevus counts at different body sites in 492 unrelated adults from both sexes, we observed that women have an increased number of naevi on the lower limbs compared to men (P=8.5x10⁻⁵), showing that a high naevus count on this site persists from childhood throughout life. Then, using data from 3,232 twins, we observed, in women, the lowest naevus count heritability on the trunk (26%), and the highest on the lower limbs (69%). Finally, we showed that, in
2,864 women, six genomic loci previously associated with both naevus count and melanoma risk (IRF4, DOCK8, MTAP, 9q31.2, KITLG, and PLA2G6) have an effect on naevus count that is body site-specific, but whose effect sizes are predominantly stronger on the lower limbs. Sex-specific genetic influence on naevus count at different sites may explain differences in site-specific melanoma incidence as well as prognosis between sexes.

Significance
The distribution of naevi, a major risk factor for melanoma development, at different body sites varies according to sex in childhood, mirroring the melanoma distribution observed in adulthood. Here, we observe an increased naevus count on the legs of adult women compared to men. In women, we also observe a different genetic contribution for naevus counts at different body sites, with a stronger effect on the legs, where known naevi and melanoma genomic loci also show, in general, a higher influence. Body site-specific genetic influence on naevus count may contribute to explain differences in site-specific melanoma incidence in women.

Introduction
Melanoma incidence at different body sites varies according to sex, with a higher incidence on the head and neck and trunk in males whilst females have a higher incidence on the lower limbs (Claus Garbe & Leiter, 2009; Krüger et al., 1992; Youl, Youlden, & Baade, 2013). Melanoma prognosis is also influenced by sex, with female patients showing longer survival than male ones (Joosse et al., 2011), and by the primary melanoma site, with upper trunk, upper arm, neck, and scalp being connected with higher risk of death, and the lower trunk, lower arms, legs, and face being linked to higher survival (C. Garbe et al., 1995).

Melanoma and naevus count share multiple genetic and environmental influences (Bauer et al., 2005; Duffy et al., 2018; Volkovova et al., 2012), and between 30-50% of melanomas arise from a naevus (Shitara et al., 2015; Shitara et al., 2014). The total body naevus count is the most powerful phenotypic marker to predict melanoma risk (Gandini et al., 2005), while naevus counts on the trunk in males and on the lower limbs in females are good predictors of sex-associated differences in melanoma risk (Krüger et al., 1992; Randi et al., 2006; Rodenas et al., 1997; Weinstock et al., 1989). Based on the existing epidemiological data and clinical observations, a theory of site-dependent susceptibility of melanocytes to malignant transformation has been proposed (Green, 1992), and studies suggest that different causal pathways may act at different body sites (Olsen et al., 2009; Siskind et al., 2005). This is further supported by the divergent pathway hypothesis (Whiteman et al., 2003) which suggests that in subjects with high melanocytic proliferative capacity (i.e., with high naevus count), the risk of melanoma is increased at those sites with the larger melanocytic population.

This article is protected by copyright. All rights reserved.
Paralleling the sex-associated differences in melanoma incidence, sex-associated differences in the
distribution of naevi has been observed in childhood: boys and girls by the age of 10 already show
different naevus distribution, with girls having more naevi on the limbs, especially on the legs, and
boys having more naevi on the head and neck and on the trunk (Autier et al., 2004; Dodd et al., 2007;
Gallagher et al., 1990). Whether these sex-specific differences in naevus distribution are genetically
determined or driven by environmental exposure is under debate. The idea that both acute and
cumulative sun-exposure contribute to the emergence of naevi is supported by multiple studies
assessing naevi number in schoolchildren living at different latitudes, which concordantly observe
that children living at the lowest latitudes had significantly more naevi than those in the highest
(Green et al., 1988; Fritschi et al., 1994; Sancho-Garnier et al., 1997). Additionally, a study of
adolescent twins from the UK suggested that the higher number of naevi in sun-exposed sites in males
could be due to a greater recreational sun exposure early in childhood (Wachsmuth et al., 2001), while
a study of white young women living in England showed that holidays in countries hotter than the UK
were associated with an increased number of naevi, particularly for sites intermittently exposed to
sunlight, such as the lower limbs (dos Santos Silva et al., 2009). However, a recent study of Danish
outdoor and indoor workers showed that the study participants, despite having different sun exposure,
did not show any difference on the number of naevi in the sun-exposed left forearm (Grandahl et al.,
2019). Furthermore, a study of boys and girls in Queensland, Australia, observed a sex-specific
difference for the number of naevi in the lower limbs that was not supported by a sex-specific
difference in sun exposure (MacLennan et al., 2003).

In order to improve performance of skin cancer prevention policies and campaigns, and to inform
cancer research, it is of utmost importance to unravel the relative importance of genetic vs
environmental factors influencing naevus development at different body sites.

In this study, we analysed a large cohort of healthy twins of European ancestry, predominately
female, to investigate factors underlying naevus count variation at four body sites (head and neck,
trunk, and upper and lower limbs). First, we tested whether the sex-associated difference in naevi
distribution at different body sites observed in childhood is also maintained in adulthood. Then, we
estimated the genetic and environmental contributions influencing naevus count variation at the
different body sites. Finally, we studied the site-specific association of naevus count distribution with
common DNA variants at five loci previously associated, in genome-wide association studies, with
both naevus count and melanoma susceptibility, i.e., IRF4, DOCK8, MTAP, 9q31.2, KITLG, and
PLA2G6 (Duffy et al., 2010, 2018; Falchi et al., 2009).
Materials and Methods

Naevus count in the TwinsUK cohort

The TwinsUK adult twin registry includes about 14,000 subjects, predominantly females, unselected for any specific disease and with similar disease and lifestyle characteristic to the general population (Andrew et al., 2001). St. Thomas’ Hospital Research Ethics Committee approved the study, and all twins provided informed written consent. Data on TwinsUK twin participants are available to bona fide researchers under managed access due to governance and ethical constraints. Raw data should be requested via the TwinsUK website (http://twinsuk.ac.uk/resources-for-researchers/access-our-data/), and requests are reviewed by the TwinsUK Resource Executive Committee (TREC) regularly.

3,923 twins with European ancestry underwent a skin examination, which included naevus count, and was performed by trained nurses at St Thomas’ Hospital, London. Briefly, the naevus count at different body sites was defined as the sum of all naevi larger than 2mm in diameter. The body sites analysed were: head and neck (H&N), trunk (back abdomen and chest), upper limbs (including shoulder), and lower limbs. The whole-body naevus count was defined as the sum of all naevi at the four aforementioned sites. We excluded from the analysis twins which were reared apart or adopted (N=20), whose zygosity was unknown (N=4), and with no naevus observed in any body sites (N=295), and outliers (N=80, individuals having a whole-body naevus count greater than 3 standard deviation the dataset mean), resulting in 3,524 individuals (N=3,296 and 228, females and males, respectively). The female (male) subset included 1,077 (79) dizygotic twin pairs, 435 (25) monozygotic twin pairs, and 272 (20) singletons (Supplementary Table 1, Supplementary Figure 1). We further removed outliers (i.e., measurements 3 standard deviation further than the dataset mean) from each of the tested naevus count and, to ensure the normality of their distribution, naevus count used for the heritability analysis and the genetic association study were quantile normalized.

Difference in sex-associated naevi distribution

From the 228 male twins we randomly selected 123 unrelated individuals which we age-matched to 369 unrelated female individuals using the matchit R package (Ho et al., 2011) (version: 3.0.2). We used the Wilcoxon’s test to assess whether there was a different distribution of naevi at different body sites between males and females, and considered this difference significant if the obtained P value passed a conservative Bonferroni-derived threshold of P<0.05/4=0.0125. To ensure the robustness of our results, we evaluated an empirical p-value using further 1,000 randomly selected sets of age-matched unrelated individuals.
Heritability analysis
We used the classic twin ACE model to estimate the contribution of additive genetic (A), common (C) and individual-specific environment (E) effects on age-adjusted naevus count variation (ACE model) in 1,512 female twin pairs (435 monozygotic and 1,077 dizygotic pairs) and 104 male twin pairs (25 monozygotic and 79 dizygotic pairs). We then compared, using the Akaike’s information criterion (AIC), the ACE model with the most parsimonious AE model, which does not include the effect of the common environment (C), and the CE and E models, which hypotheses that the trait variation is completely dependent on the effects of the environment. The models along with their 95% confidence intervals and AIC, were estimated using the mets R package (Scheike et al., 2014) (version: 1.2.5).

Genetic association study
Genotyping was performed in 2,864 females from the TwinsUK cohort with a combination of Illumina arrays (HumanHap300, HumanHap610, 1M-Duo and 1.2M-Duo 1M) and imputation was carried out using the Michigan Imputation Server and the Haplotype Reference Consortium (HRC version r1.1) panel (the Haplotype Reference Consortium, 2016). We selected ten SNPs at the IRF4, DOCK8, MTAP, 9q31.2, KITLG, and PLA2G6 loci which were previously associated with naevus count (Duffy et al., 2010, 2018; Falchi et al., 2009), and extended this set with 2,435 SNPs in high linkage disequilibrium with them (r^2 >0.8, distance limit 500 kb; EUR populations), as detected using LDLink (Machiela & Chanock, 2015). We then used for the association testing 1,836 out of the 2,435 SNPs, which were available in our panel and met the following conditions: call rate ≥95%, minor allele frequency (MAF) ≥1% and Hardy–Weinberg equilibrium test with P ≥ 1 × 10^{-9} (Supplementary Table 2). To take into account the non-independence of the twin data, the association with naevus count on the whole body and on the four body sites was evaluated using GEMMA (Zhou & Stephens, 2014) (version 0.97), assuming an additive genetic model and including age at visit and the first five principal components assessed on the genomic data as covariates. Given the high correlation between both the site-specific naevus count and the SNPs in strong linkage disequilibrium, we used the method introduced by Conneely and Boehnke (Conneely & Boehnke, 2007) (P_{ACT}) to calculate adjusted P values accounting for multiple and correlated tests. P_{ACT} yields to the same accuracy attained by permutation tests, providing an unbiased test of the null hypothesis.

Results
The distribution of naevi on the lower limbs varies according to sex
Using data from 123 randomly-selected unrelated male and a subset of 369 age-matched unrelated female members of our cohort (Supplementary Figure 2), we observed a sex-associated difference in naevi distribution on the lower limbs, with females showing a statistically significantly higher number of naevi on the lower limbs (mean N=6.7 and 4.1, in females and males, respectively; P = 8.5x10^{-5},
Wilcoxon’s test, **Figure 1**), which was confirmed by a permutation test (eP = 5.0x10^-3). Males showed a higher number of naevi on the trunk (mean N=0.48 and 0.94, in females and males, respectively), although this was only nominally significant (P=0.02, Wilcoxon’s test) and not supported by the permutation test in this small dataset (eP > 0.05).

**The heritability of naevus count varies according to body sites in women**

The best fitting model for site-specific heritability of naevus count in women was predominantly the full ACE model (Supplementary Table 3), suggesting that both unique (E) and shared environmental factors (C) play a role in its variability. Additive genetic effects accounted for 59% of the variance of the whole body naevus count, while environmental effects explained the remaining 41% (Table 1). A highly variable influence of environmental versus additive genetic factors accounted for the variability of naevus count at individual sites, with the trunk showing the lowest genetic influence (A=26%), and the lower limbs showing the largest (A=69%; Table 1).

In males, the AIC values indicated a better fit for the more parsimonious AE and CE models (Supplementary Table 3), most likely due to the small male sample size. Indeed, while the female subset included 1,512 twin pairs (435 monozygotic and 1,077 dizygotic pairs), the male subset was composed by 104 twin pairs (25 monozygotic and 79 dizygotic pairs). The additive genetic effects accounted for more than 67% of the naevus count variation in whole body and at all the studied sites, apart from the lower limbs, where the naevus count distribution was completely explained by environmental effects (Table 1).

**The effect of known naevus loci varies according to body sites in females**

Using data on 2,864 female individuals for whom both phenotypical and genomic data was available, we confirmed significant associations between naevus count on whole body and **MTAP, PLA2G6**, and the 9q31.2 region, but failed to identify associations with **IRF4, DOCK8**, and **KITLG**. We hypothesise that we were not able to replicate the association with **IRF4** because the effect of these variants on the H&N plus trunk and the lower limbs, which include 26% and 31% of the total naevus count, have an opposite direction, therefore nullifying the effect on the whole body. On the other hand, it is likely that **DOCK8** and **KITLG** exert a small effect on naevus count, detectable only by a large sample, as that reached in the recent meta-analysis study of 52,506 individuals that lead to their identification (Duffy et al., 2018).

When studying loci-specific effect on different body sites, we observed that all tested loci apart from **DOCK8, MTAP, and KITLG** where significantly associated with the number of naevi on the lower limbs, but only **PLA2G6** was exerting a significant effect on naevus on the trunk (adjP > 0.05, Table 2). The naevus distribution on the H&N was associated with DNA variants at the **IRF4** and **MTAP**

This article is protected by copyright. All rights reserved.
loci, while the naevus on the upper limbs was significantly associated with DNA variants at the DOCK8, MTAP and PLA2G6 loci (Table 2).

Discussions
Genome-wide association studies have shown that melanoma and naevus count share a common genetic background (Duffy et al., 2018). According to Whiteman’s “divergent pathway hypothesis”, subjects with high melanocyte proliferation are more likely to develop melanoma at those body sites showing high naevus count (Whiteman et al., 2003).

We show, here, that the number of naevi on the lower limbs is almost double in females compared to males. These results are in line with what has been previously observed in children (Autier et al., 2004; Dodd et al., 2007; Gallagher et al., 1990) and adults (Krüger et al., 1992) thus suggesting that a sex-associated difference in naevi distribution on the lower limbs persists throughout life.

We confirmed a strong heritability of 60-70% on whole body naevus count in women (Wachsmuth et al., 2001), and observed sex-specific heritability at different sites. The genetic influence on naevus count was higher on the lower limbs and lower on the trunk (69% and 26%, respectively). In males, significant heritability was detected at all body sites (>67%) apart from the lower limbs, where we could not observe any genetic influence – perhaps due to the small male sample size. Our results support the hypothesis that the larger number of naevi on the female lower limbs is unlikely due to higher sun exposure alone (Bataille, 2013), and indicate that naevus development and persistence on the lower limbs with age is actually under significant sex-specific genetic control.

The association between variants at the IRF4, DOCK8, MTAP, 9q31.2, KITLG, and PLA2G6 loci and both naevus count and melanoma development has been largely investigated (Duffy et al., 2010, 2018; Falchi et al., 2009). However, few studies explored whether these variants have a different contribution on melanoma development at different body site (Kvaskoff et al., 2011; Potrony et al., 2017) and none of them explored their effect on naevi distribution. Apart from a weak significant association between DOCK8 and naevus count in the upper limbs (adjP=0.023), we could not find any other significant association (adjP < 0.05) between naevus count and both DOCK8 and KITLG, most likely due to the small effect these genes exert on naevus count, and that would require a much larger dataset for its identification. However, we showed that, in females, all the other studied loci, apart from MTAP, concordantly affect naevus count on the lower limbs, while their effects on the other body sites was locus-specific (Table 2). It has been observed, in mixed-sex cohorts, that variants at the IRF4 locus contribute to melanoma development both via chronic sun exposure and via melanocytic proliferative capacity (Gibbs et al., 2016), and that they influence melanoma survival as well as the site of the primary tumour, increasing the risk of developing melanoma on the H&N but
This article is protected by copyright. All rights reserved.
Acknowledgments
TwinsUK is funded by the Wellcome Trust, Medical Research Council, European Union, the National Institute for Health Research (NIHR)-funded BioResource, Clinical Research Facility and Biomedical Research Centre based at Guy’s and St Thomas’ NHS Foundation Trust in partnership with King’s College London.

Figure Legends
Figure 1. Naevus count distribution by sex at different body sites. The mean number of naevi (μ) and the P values, evaluated by means of the Wilcoxon’s test, are reported.

Supplementary Figure Legends
Supplementary Figure 1. Age distribution by sex in the entire study sample. Distribution were evaluated for 3,296 females and 228 of European ancestry. The P value was evaluated by means of the Wilcoxon’s test.

Supplementary Figure 2. Age distribution by sex in the age-matched dataset. The P value, evaluated by means of the Wilcoxon’s test, shows a perfect age-match between male and female set.

Conflict of interest
The authors declare that they have no conflict of interest.

References


This article is protected by copyright. All rights reserved.


This article is protected by copyright. All rights reserved.


https://doi.org/10.17795/ijcp-5079


This article is protected by copyright. All rights reserved.


This article is protected by copyright. All rights reserved.
### Tables

**Table 1.** Estimates of the percentage of age-adjusted naevus count variance in different body sites due to additive genetic (A), common (C), and individual-specific (E) environmental effects along with their 95% confidence intervals (CI, in brackets). We reported the estimates for the best fitting model (ACE, AE, CE, E) as evaluated using the AIC criterion. Each model was generated using data collected in 1,512 female twin pairs (435 monozygotic and 1,077 dizygotic pairs) or 104 male twin pairs (25 monozygotic and 79 dizygotic pairs).

<table>
<thead>
<tr>
<th>Sex</th>
<th>Body site</th>
<th>Model</th>
<th>A (95% CI)</th>
<th>C (95% CI)</th>
<th>E (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Whole body</td>
<td>ACE</td>
<td>59.0 (47.8, 70.2)</td>
<td>15.9 (6.1, 25.8)</td>
<td>25.1 (21.6, 28.6)</td>
</tr>
<tr>
<td>Females</td>
<td>H&amp;N</td>
<td>ACE</td>
<td>33.5 (16.6, 50.3)</td>
<td>14.5 (2.1, 27.0)</td>
<td>52.0 (45.2, 58.8)</td>
</tr>
<tr>
<td></td>
<td>Trunk</td>
<td>ACE</td>
<td>25.9 (11.4, 40.4)</td>
<td>29.6 (18.6, 40.6)</td>
<td>44.5 (38.7, 50.3)</td>
</tr>
<tr>
<td></td>
<td>Upper limbs</td>
<td>ACE</td>
<td>54.4 (41.4, 67.3)</td>
<td>12.5 (1.8, 23.2)</td>
<td>33.1 (28.5, 37.7)</td>
</tr>
<tr>
<td></td>
<td>Lower limbs</td>
<td>AE</td>
<td>69.0 (65.0, 72.9)</td>
<td>-</td>
<td>31.0 (27.1, 35.0)</td>
</tr>
<tr>
<td></td>
<td>Whole body</td>
<td>AE</td>
<td>70.8 (56.7, 84.9)</td>
<td>-</td>
<td>29.2 (15.1, 43.3)</td>
</tr>
<tr>
<td></td>
<td>H&amp;N</td>
<td>AE</td>
<td>72.1 (56.3, 87.9)</td>
<td>-</td>
<td>27.9 (12.1, 43.7)</td>
</tr>
<tr>
<td>Males</td>
<td>Trunk</td>
<td>AE</td>
<td>67.3 (50.6, 84.1)</td>
<td>-</td>
<td>32.7 (15.9, 49.4)</td>
</tr>
<tr>
<td></td>
<td>Upper limbs</td>
<td>AE</td>
<td>76.1 (63.3, 89.0)</td>
<td>-</td>
<td>23.9 (11.0, 36.7)</td>
</tr>
<tr>
<td></td>
<td>Lower limbs</td>
<td>CE</td>
<td>-</td>
<td>55.6 (42.1, 69.2)</td>
<td>44.4 (30.8, 57.9)</td>
</tr>
</tbody>
</table>

*Despite the ACE model being the best model according to the AIC, the estimate for the C component was not significative, and the AE model has been reported instead. For the sake of completeness, the ACE results for the model were: A=57.6% (95%CI: 44.7-70.5%), C=10.2% (95%CI: -0.6-21.1%), E=32.2% (95%CI: 27.8%-36.6%).*
Table 2. Results of the genetic association study 2,864 female twins. For each body site/locus, we report the top-associated SNP, along with its coordinates (build: GRCh37), effect and non-effect allele (A1/A0) and effect allele’s frequency (AF), effect size (β), standard error (SE), and association P value evaluated via likelihood ratio tests (P). Adjusted-P values (adjP) were evaluated with P_{ACT} taking into account the number of tested SNPs and body sites (Conneely & Boehnke, 2007).

<table>
<thead>
<tr>
<th>Locus</th>
<th>Body Site</th>
<th>SNP</th>
<th>Coordinate</th>
<th>A1/A0</th>
<th>AF</th>
<th>β</th>
<th>SE</th>
<th>P</th>
<th>adjP</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRF4</td>
<td>Whole body</td>
<td>rs12203592</td>
<td>chr6:396321</td>
<td>T/C</td>
<td>0.19</td>
<td>0.041</td>
<td>0.044</td>
<td>0.350</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>H&amp;N</td>
<td>rs62389423</td>
<td>chr6:421281</td>
<td>A/G</td>
<td>0.16</td>
<td>-0.156</td>
<td>0.046</td>
<td>6.0x10^{-4}</td>
<td>0.013</td>
</tr>
<tr>
<td></td>
<td>Trunk</td>
<td>rs3778607</td>
<td>chr6:403799</td>
<td>G/A</td>
<td>0.55</td>
<td>-0.070</td>
<td>0.031</td>
<td>0.024</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>Upper limbs</td>
<td>rs62389424</td>
<td>chr6:422631</td>
<td>A/C</td>
<td>0.17</td>
<td>0.064</td>
<td>0.043</td>
<td>0.142</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>Lower limbs</td>
<td>rs12203592</td>
<td>chr6:396321</td>
<td>T/C</td>
<td>0.19</td>
<td>0.211</td>
<td>0.045</td>
<td>2.7x10^{-6}</td>
<td>7.5x10^{-5}</td>
</tr>
<tr>
<td>DOCK8</td>
<td>Whole body</td>
<td>rs581731</td>
<td>chr9:206838</td>
<td>C/A</td>
<td>0.47</td>
<td>-0.073</td>
<td>0.028</td>
<td>9.4x10^{-1}</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>H&amp;N</td>
<td>rs581731</td>
<td>chr9:206838</td>
<td>C/A</td>
<td>0.47</td>
<td>-0.049</td>
<td>0.028</td>
<td>0.085</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>Trunk</td>
<td>rs3008099</td>
<td>chr9:177034</td>
<td>G/T</td>
<td>0.36</td>
<td>0.094</td>
<td>0.034</td>
<td>5.3x10^{-3}</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>Upper limbs</td>
<td>rs581731</td>
<td>chr9:206838</td>
<td>C/A</td>
<td>0.47</td>
<td>-0.090</td>
<td>0.028</td>
<td>1.2x10^{-2}</td>
<td>0.023</td>
</tr>
<tr>
<td></td>
<td>Lower limbs</td>
<td>rs471897</td>
<td>chr9:270224</td>
<td>T/G</td>
<td>0.34</td>
<td>-0.046</td>
<td>0.030</td>
<td>0.128</td>
<td>ns</td>
</tr>
<tr>
<td>MTAP</td>
<td>Whole body</td>
<td>rs7860576</td>
<td>chr9:21714920</td>
<td>C/T</td>
<td>0.48</td>
<td>-0.131</td>
<td>0.029</td>
<td>4.2x10^{-9}</td>
<td>1.1x10^{-6}</td>
</tr>
<tr>
<td></td>
<td>H&amp;N</td>
<td>rs7852450</td>
<td>chr9:21825075</td>
<td>C/T</td>
<td>0.52</td>
<td>-0.118</td>
<td>0.028</td>
<td>2.9x10^{-5}</td>
<td>7.4x10^{-4}</td>
</tr>
<tr>
<td></td>
<td>Trunk</td>
<td>rs7029077</td>
<td>chr9:21682302</td>
<td>C/G</td>
<td>0.14</td>
<td>0.079</td>
<td>0.041</td>
<td>0.057</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>Upper limbs</td>
<td>rs6475574</td>
<td>chr9:21736052</td>
<td>T/C</td>
<td>0.51</td>
<td>-0.112</td>
<td>0.028</td>
<td>6.3x10^{-5}</td>
<td>1.5x10^{-3}</td>
</tr>
<tr>
<td></td>
<td>Lower limbs</td>
<td>rs7860576</td>
<td>chr9:21714920</td>
<td>C/T</td>
<td>0.48</td>
<td>-0.082</td>
<td>0.029</td>
<td>5.0x10^{-5}</td>
<td>ns</td>
</tr>
<tr>
<td>9q31.2</td>
<td>Whole body</td>
<td>rs10816590</td>
<td>chr9:110700471</td>
<td>G/C</td>
<td>0.59</td>
<td>-0.089</td>
<td>0.029</td>
<td>2.0x10^{-3}</td>
<td>0.036</td>
</tr>
<tr>
<td></td>
<td>H&amp;N</td>
<td>rs10816591</td>
<td>chr9:110700994</td>
<td>A/G</td>
<td>0.59</td>
<td>-0.059</td>
<td>0.029</td>
<td>0.041</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>Trunk</td>
<td>rs7026539</td>
<td>chr9:110707964</td>
<td>T/C</td>
<td>0.59</td>
<td>0.041</td>
<td>0.029</td>
<td>0.154</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>Upper limbs</td>
<td>rs10816597</td>
<td>chr9:110713179</td>
<td>C/T</td>
<td>0.39</td>
<td>-0.078</td>
<td>0.029</td>
<td>6.2x10^{-3}</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>Lower limbs</td>
<td>rs10816590</td>
<td>chr9:110700471</td>
<td>G/C</td>
<td>0.59</td>
<td>-0.105</td>
<td>0.030</td>
<td>3.8x10^{-4}</td>
<td>8.4x10^{-3}</td>
</tr>
<tr>
<td>KITLG</td>
<td>Whole body</td>
<td>rs1492349</td>
<td>chr12:88854647</td>
<td>A/G</td>
<td>0.92</td>
<td>0.132</td>
<td>0.052</td>
<td>0.011</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>H&amp;N</td>
<td>rs78835149</td>
<td>chr12:88804217</td>
<td>C/G</td>
<td>0.27</td>
<td>0.095</td>
<td>0.038</td>
<td>0.013</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>Trunk</td>
<td>rs2639099</td>
<td>chr12:89008364</td>
<td>T/C</td>
<td>0.06</td>
<td>0.106</td>
<td>0.061</td>
<td>0.079</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>Upper limbs</td>
<td>rs7486790</td>
<td>chr12:88816594</td>
<td>G/T</td>
<td>0.84</td>
<td>0.107</td>
<td>0.038</td>
<td>4.8x10^{-3}</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>Lower limbs</td>
<td>rs7974506</td>
<td>chr12:88848006</td>
<td>G/A</td>
<td>0.92</td>
<td>0.138</td>
<td>0.052</td>
<td>8.3x10^{-3}</td>
<td>ns</td>
</tr>
<tr>
<td>PLA2G6</td>
<td>Whole body</td>
<td>rs132941</td>
<td>chr22:38545942</td>
<td>C/T</td>
<td>0.44</td>
<td>-0.145</td>
<td>0.029</td>
<td>4.8x10^{-3}</td>
<td>1.4x10^{-3}</td>
</tr>
<tr>
<td></td>
<td>H&amp;N</td>
<td>rs5756914</td>
<td>chr22:38502639</td>
<td>C/T</td>
<td>0.53</td>
<td>-0.077</td>
<td>0.029</td>
<td>7.5x10^{-4}</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>Trunk</td>
<td>rs2076372</td>
<td>chr22:38474965</td>
<td>T/C</td>
<td>0.28</td>
<td>-0.100</td>
<td>0.032</td>
<td>2.0x10^{-3}</td>
<td>0.037</td>
</tr>
<tr>
<td></td>
<td>Upper limbs</td>
<td>rs132972</td>
<td>chr22:38562056</td>
<td>C/T</td>
<td>0.54</td>
<td>-0.104</td>
<td>0.028</td>
<td>1.9x10^{-4}</td>
<td>4.4x10^{-3}</td>
</tr>
<tr>
<td></td>
<td>Lower limbs</td>
<td>rs132941</td>
<td>chr22::38545942</td>
<td>C/T</td>
<td>0.45</td>
<td>-0.141</td>
<td>0.029</td>
<td>1.5x10^{-6}</td>
<td>4.3x10^{-5}</td>
</tr>
</tbody>
</table>

ns=not significative (adjP > 0.05)