




Genetics plays a role in nevi distribution in women

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“it would be crucial to translate these results to melanoma research, investigating whether these pleiotropic *loci*, as well as any other associated locus, are exerting an effect on melanoma susceptibility that is sex dependent.”

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Melanoma is a tumor whose incidence has increased steadily in the last 50 years in fair-skinned populations. Despite representing less than 5% of all skin cancers, melanoma accounts for the majority of skin cancer deaths [1].

Men have a poorer prognosis compared with women and, in many countries, melanoma incidence is higher in women [2,3]. These sex differences could be due to both behavioral and biological factors, as reviewed by Schwartz *et al.* [3]. Behavioral factors influenced by gender may include, among others, sunbed use, recreational UV exposure, use of sun protection and skin awareness. The increased risk in women appears to be counterbalanced by increased protection and early diagnosis, which allows for the detection of thinner tumors, improving the survival rate. However, biological factors, such as differences in the underlying genetic risk architecture, can also be at play [3]. Males and females also present different primary tumor sites, with a higher incidence on the head, neck and torso in males and on the legs in females. It is not yet clear whether this could be due to sex differences in behaviors, genetic make-up, or their interplay [3].

Melanoma and nevi both derive from the proliferation of melanocytes, which is uncontrolled in the former and benign in the latter. It is estimated that between 20 and 50% of melanomas arise from a nevus [4]. The total body nevus count is the most powerful phenotypic marker to predict melanoma risk [5], and melanoma and nevi share multiple genetic and environmental influences [6]. For instance, studies suggest that early exposure to UV light plays a role in inducing both nevi and melanoma (e.g., [7]), and a recent genome-wide meta-analysis by Duffy *et al.* identified pleiotropic effects on melanoma risk of five genetic *loci* (namely: *IRF4*, *DOCK8*, *MTAP*, 9q31.2, *KITLG* and *PLA2G6*) influencing nevus count [8].

Mirroring what is already observed for melanoma primary site, sex differences in nevus distribution are observed at different body sites from childhood onward, with females having more nevi on the legs, and males having more nevi on the head, neck and torso [9,10]. Interestingly, nevus count on the torso in males and on the legs in females are better predictors of overall melanoma risk than nevus count at any other site [9]. These sex differences in nevus counts could be due to both behavioral and genetic factors, with observational studies supporting both hypotheses. For instance, a small study of men and women living in Spain failed to find any difference in nevus count on the legs, likely due, according to the authors, to the fact that, in this country, both men and women commonly expose this site [11]. However, a much larger study carried out in Queensland, Australia, where again children of both sexes commonly expose their legs, observed an increased number of nevi on the legs in girls compared with boys [12]. Furthermore, sex chromosomes may also play a role in nevus distribution and number. For instance, individuals with Turner syndrome (45,X monosomy) show an increased number of nevi [13], and a study exploring genes differentially expressed in Turner syndrome versus healthy women (46,XX) identified, among the others, an autosomal gene (*DOCK7*) associated to the distribution and function of melanocytes in mice [14]. Another hypothesis is that the observed differences in body site nevus distribution between sexes could

be due to sex-specific mechanisms driving melanocyte migration and differentiation during embryogenesis, and which are likely to continue affecting nevi and melanoma behavior throughout one's lifetime, an aspect also worth investigating.

To investigate the role of genetic and environmental factors in these site-specific differences in women, we took advantage of nevus count data available for 1512 female twin pairs of European ancestry. Twins studies can estimate the proportion of the variability of a trait that is caused by genetic effect and by environmental factors [15]. We showed that 69% of the nevus count variability on the legs – the site more common for melanoma in women – could be explained by genetic effects, and only 31% was due to environmental factors [10]. For comparison, on the torso, where melanoma incidence is lower in females, genetic effects were the lowest and responsible for only 26% of the nevus count variability in the female twins. In the same group of female twins, genetics explained 34% of the nevus count variability on the head and neck, and 54% in the arms.

Next, we investigated whether genetic variants at the six pleiotropic melanoma and nevus count *loci* identified by Duffy *et al.* [8] had a different effect on nevus count distribution at different body sites in 2864 women. We observed that genetic variants at the *IRF4*, 9q31.2, and *PLA2G6* *loci* influenced the number of nevi on the legs. Nevus count on the arms was significantly associated with variants at the *DOCK8*, *MTAP* and *PLA2G6* *loci*, while nevus count on the head and neck were associated with variants at the *IRF4* and *MTAP* *loci*. Only the *PLA2G6* locus was associated with nevus count distribution on the torso [10].

Our results suggest that, in women, increased nevus count on the legs is under significant genetic control, and unlikely due to higher UV exposure alone, as already suggested [16], and that the impact of genetics on nevus count differs according to body sites.

In summary, current research demonstrates that melanoma susceptibility and survival are strongly connected with biological sex, which appears to influence also the site of the primary tumor [3]. Analogously, nevus count distribution at different body sites seems to have a sex-specific pattern, which we have shown to be under genetic influence [10], albeit only in women.

In the future, it would be important, first and foremost, to assess whether nevus count distribution is also under a site-specific genetic control in men, which we could not test due to the small number of men in our cohort, and to extend our investigation to the role of sex chromosomes. Then, it would be crucial to translate these results to melanoma research, investigating whether these pleiotropic *loci*, as well as any other associated locus, are exerting an effect on melanoma susceptibility that is sex dependent. Indeed, few studies have investigated genetic differences according to sex in melanoma (reviewed in [3]). This would include performing sex-stratified genome-wide association studies or candidate gene analyses, as well as testing for gene-by-sex interactions. Of course, this sex-stratified approach of investigation could be extended to other melanoma risk factors, such as hair and eye color, or tanning ability. In our view, these approaches will allow dissection of the underlying mechanisms responsible for the observed differences in melanoma susceptibility between sexes, and drive intervention strategies targeted to men and women distinctly to improve therapeutic outcomes.

Author contributions

A Visconti wrote the manuscript. M Sanna contributed to the literature review. All authors read and approved the final version of the manuscript.

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