

## REVIEW

# The study of nevi in children: Principles learned and implications for melanoma diagnosis

Alon Scope, MD,<sup>a,b</sup> Michael A. Marchetti, MD,<sup>a</sup> Ashfaq A. Marghoob, MD,<sup>a</sup> Stephen W. Dusza, DrPH,<sup>a</sup>  
Alan C. Geller, MPH,<sup>c</sup> Jaya M. Satagopan, PhD,<sup>d</sup> Martin A. Weinstock, MD, PhD,<sup>e,f,g</sup>  
Marianne Berwick, PhD,<sup>h</sup> and Allan C. Halpern, MD<sup>a</sup>  
*New York, New York; Tel Aviv, Israel; Boston, Massachusetts; Providence, Rhode Island;  
and Albuquerque, New Mexico*

Melanocytic nevi are a strong phenotypic marker of cutaneous melanoma risk. Changes in nevi during childhood and adolescence make these prime periods for studying nevocogenesis. Insights gained by the study of nevi in childhood have implications for melanoma detection in both adults and children. A more comprehensive understanding of the morphologic characteristics of nevi in different anatomic locations, in association with the patient's age and pigmentary phenotype may aid in the identification of melanomas. When monitoring melanocytic lesions over time, it is essential to differentiate normal from abnormal change. This review summarizes the rapidly expanding body of literature relevant to nevus phenotype, particularly in the context of our experience with the Study of Nevi in Children (SONIC) Project. (J Am Acad Dermatol <http://dx.doi.org/10.1016/j.jaad.2016.03.027>.)

**Key words:** adolescence; childhood; dermoscopy; detection; melanoma; nevi; nevocogenesis.

## INTRODUCTION

In 2010, >49,000 individuals were estimated to have died from melanoma worldwide.<sup>1</sup> Nevi are among the strongest phenotypic markers of melanoma risk.<sup>2</sup> Diagnosis often relies on differentiating a melanoma from the patient's many nevi. This can be challenging because nevi are heterogeneous and their morphology varies depending on the patient's age, pigmentary phenotype, ultraviolet radiation exposure, and genotype, as well as the anatomic location and potential for change.<sup>3-14</sup> While current aids for melanoma detection rely on morphology to distinguish nevi from melanomas, such as ABCDE criteria (*asymmetry, border irregularity, color variation, diameter* > 6 mm, and *evolving*) and

### Abbreviations used:

CI:	confidence interval
Mc1R:	melanocortin-1 receptor
OR:	odds ratio
RHC:	red hair color
SONIC:	Study of Nevi in Children

dermoscopy,<sup>15-19</sup> patient-related factors are not included in diagnostic algorithms. A more comprehensive understanding of the natural history of nevi and variations in their patterns is needed to improve melanoma detection.<sup>20</sup>

The first 2 decades of life are notable for appearance and growth of nevi, making this an important

From the Dermatology Service,<sup>a</sup> Department of Medicine, and the Department of Epidemiology and Biostatistics,<sup>d</sup> Memorial Sloan Kettering Cancer Center, New York; Department of Dermatology,<sup>b</sup> Sheba Medical Center and Sackler School of Medicine, Tel Aviv University; Harvard School of Public Health, Social and Behavioral Sciences,<sup>c</sup> Boston; Dermatoepidemiology Unit,<sup>e</sup> Veteran's Affairs Medical Center and Department of Dermatology,<sup>f</sup> Rhode Island Hospital, and Departments of Dermatology and Epidemiology,<sup>g</sup> Brown University, Providence; and the Division of Epidemiology and Biostatistics,<sup>h</sup> University of New Mexico, Albuquerque.

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Correspondence to: Allan C. Halpern, MD, Dermatology Service, Memorial Sloan Kettering Cancer Center, 16 E 60th St, New York, NY 10022. E-mail: [halperna@mskcc.org](mailto:halperna@mskcc.org).

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period for studying neovogenesis.<sup>21-23</sup> Insights gained by the study of nevi in childhood have implications for melanoma detection in both adults and children. The Study of Nevi in Children (SONIC), a cohort in Framingham, Massachusetts,<sup>11-13,24-36</sup> is a population-based study that documents the dermoscopic and clinical evolution of nevi in childhood and adolescence over time. Herein, we summarize a rapidly expanding body of literature, particularly in the context of our experience with SONIC, regarding patient-related factors that contribute to nevus phenotype and their implications for melanoma diagnosis.

### Age-related prevalence of dermoscopic patterns of nevi

The predominant dermoscopic pattern can be predicted based on a patient's age. In early childhood, a globular nevus pattern is most prevalent, while in adulthood, a reticular pattern predominates (Table I).<sup>10</sup> In the SONIC cohort, we observed a gradual decline in the percentage of globular nevi and an increase in that of reticular nevi during the second decade of life.<sup>12,31,37</sup> A similar trend was observed in a pediatric cohort study from Italy.<sup>38</sup> Cross-sectional analysis of the dermoscopic patterns of nevi on the trunk by age is consistent with these longitudinal observations (Table I).

Another dermoscopic pattern with an age-dependent prevalence is the peripheral globular pattern. This nevus morphology is associated with growth,<sup>39</sup> with large junctional nests at the periphery on examination by histopathology and reflectance confocal microscopy.<sup>40</sup> Among SONIC participants aged 14 ( $n = 345$ ), this pattern was observed in approximately 3% of back nevi ( $n = 1152$ ) but was rare (<0.5%) in leg nevi ( $n = 290$ ; unpublished data). Zalaudek et al<sup>10</sup> noted the relative frequency of nevi with peripheral globules on the trunk among patients seen in pigmented lesion clinics to be 9% in the first decade, 5% in the second decade, 4% in the third decade, and 1.5% in the fourth decade of life, after which the frequency became <1%.

**Implications for clinical practice.** A new globular nevus is less common with advanced age (Fig 1). Recently, a subtype of melanoma termed “nested melanoma of the elderly” was reported.<sup>41-44</sup> These melanomas have irregularly distributed globules on dermoscopic examination, corresponding to

a “clod” pattern of large compact nests on confocal microscopy, and to large intraepidermal nests on histopathologic examination.<sup>41-44</sup> Early recognition is important given the observation of Beer et al<sup>45</sup> that melanomas harboring a predominantly globular pattern, with large nests and aggregates on histopathology, grow faster than melanomas that show a predominantly reticular pattern, with lentiginous or small-nested pattern on histopathology.

The age-dependent prevalence of nevi with peripheral globules has clinical implications (Fig 2). In the second to third decades of life,<sup>10</sup> patients with nevi with a peripheral rim of globules do not require specific intervention. In patients >30 years of age, nevi with a peripheral rim of globules without any other melanoma-specific criteria

should be digitally monitored to ensure symmetric enlargement. The growth rate of nevi with peripheral globules is comparable to the growth rate of some melanomas.<sup>33,45</sup> Unlike melanoma, nevi with peripheral globules grow symmetrically and do not develop any new structures or colors as they grow, lack melanoma-specific structures, and the peripheral globules become smaller and eventually disappear once nevus growth ceases. In patients >50 years of age, nevi with peripheral globules are rare, the incidence of melanoma among new or changing lesions is relatively high, and this dermoscopic pattern should prompt a clinician to consider obtaining a biopsy specimen of the lesion.<sup>10,46</sup>

### Anatomic site-related prevalence of dermoscopic patterns of nevi

In SONIC, we observed that globular-patterned nevi occur more frequently on the upper part of the body, where they tend to be larger in diameter; on the lower trunk and extremities, the predominant nevus pattern becomes increasingly reticular and nevi tend to be smaller.<sup>12,31</sup> At 11 years of age, nevi were more likely to be globular on the upper than on the lower back (odds ratio [OR] = 2 [95% confidence interval {CI}, 1.6-2.6];  $P < .001$ ).<sup>12</sup> At 14 years of age, compared to referent homogeneous nevi, globular nevi were more commonly observed on the back than the legs (OR = 29.4 [95% CI, 9.5-90.7];  $P < .001$ ), whereas reticular nevi were less likely to be observed on the back than the legs (OR = 0.7 [95% CI, 0.5-0.8];  $P = .001$ ).<sup>31,37</sup> Similarly, congenital melanocytic nevi

### CAPSULE SUMMARY

- Melanocytic nevi are strong risk markers for melanoma.
- We summarize recent insights regarding the natural history of nevi and patient-related factors that contribute to nevus phenotype, such as age, anatomic site, and skin color.
- Insights gained from studies of benign nevi can aid in the identification of potential melanomas.

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