## RAS pathway influences the number of melanocytic nevi in cardiofaciocutaneous and Costello syndromes

*To the Editor*: The number of melanocytic nevi is one of the strongest risk factors for melanoma,[1] yet the reasons for the interpersonal variability in this number are largely unknown. Both nevi and melanoma show somatic mutations in the RAS pathway components, most commonly in *BRAF*.[2] Germline mutations in these same genes cause a group of developmental syndromes termed RASopathies,[3] some of which characteristically display melanocytic nevi.[4] However, the effects of germline RAS pathway mutations on the number of nevi are poorly understood.

To determine how the number of melanocytic nevi is influenced by the RAS pathway, we analyzed the numbers of nevi in cardiofaciocutaneous syndrome (CFC) and Costello syndrome (CS). CFC is caused by mutations in the downstream elements of the RAS pathway, including *BRAF*, *MAP2K1*, and *MAP2K2*, or, rarely, *KRAS*,[5,6] whereas CS results from mutations in an upstream core component of the pathway, *HRAS* (Fig 1).[7]

The institutional review board at the University of California Davis approved the study. After informed consent, 16 individuals with CFC and 24 with CS were enrolled.[8] Photography of nevi was performed (Canfield Scientific, Parsippany, NJ). The photographs were examined for the number of nevi by 2 authors independently and without knowledge of the mutation status. Fitzpatrick skin phototype was determined based on the photographs and a questionnaire regarding tendency to burn and tan. A 2-sample *t* test and linear regression models were used.

The mean age for individuals with CFC was 15.1 years (range, 6-35 years) and for those with CS was 14.5 years (range, 6-31 years).[8] The majority of individuals with CFC reported a *BRAF* mutation (*BRAF* in 13/16 [81.3%], *MAP2K1* in 1/16 [6.3%], *MAP2K2* in 1/16 [6.3%], and unknown in 2/16 [12.5%]), and the majority of individuals with CS reported an *HRAS* mutation (p.G12S in 16/25 [64.0%]; p.G12C in 2/25 [8.0%]; p.G12A, p.G13C, p.G13D, p.A146V, and p.K117R in 1 each/25 [4.0%]; and unknown in 2/25 [6.3%]).[8]

A marked difference was noted in the number of nevi in CFC versus CS (Fig 2 and Table I). The average number of nevi on the back was 47.8 in CFC (standard error of the men [SEM], 14.0) and 8.1 in CS (SEM, 1.8; $P = .002$). The number of nevi in CS corresponds to published population-based data of 8.4 nevi on average on the back of children and

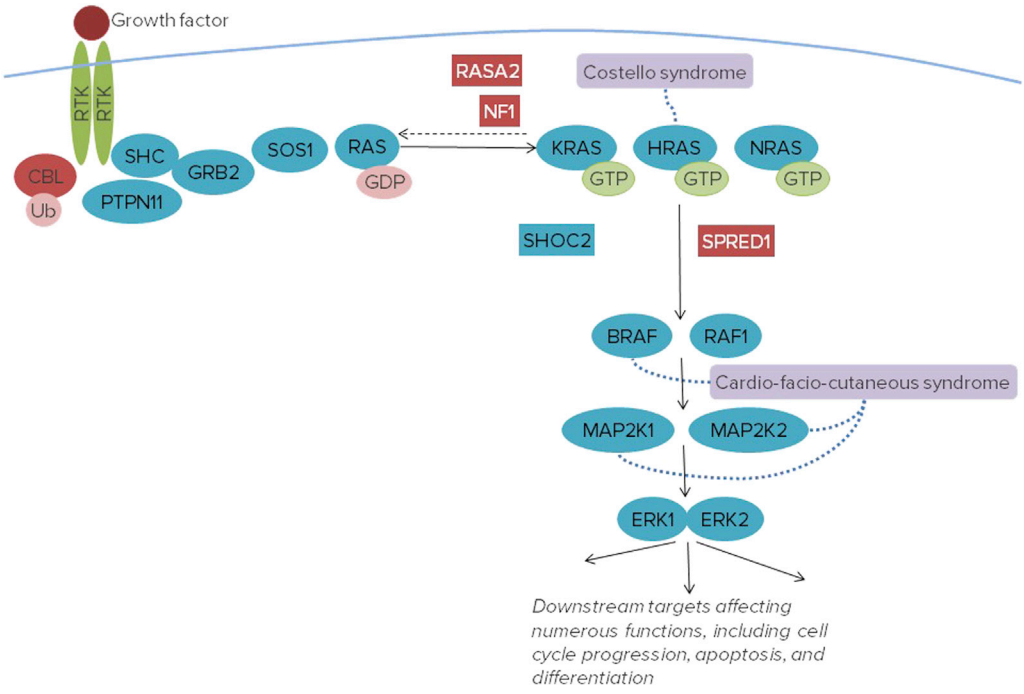


**Fig 1.** The RAS pathway showing genes mutated in patients with cardiofaciocutaneous syndrome and Costello syndrome in this study.

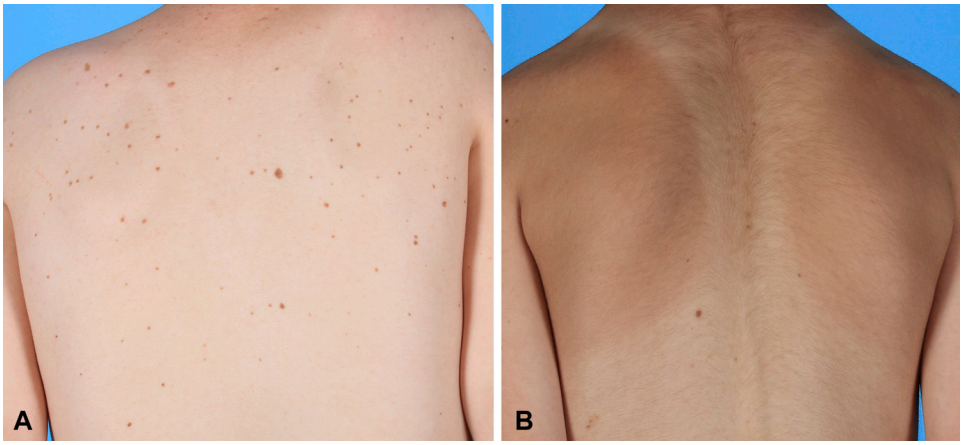


**Fig 2.** Increase in the number of nevi in (**A**) an individual with cardiofaciocutaneous syndrome compared with (**B**) an individual with Costello syndrome. Both individuals are women ages 22 to 23 years.

**Table I.** Number of nevi in CFC and CS

| Characteristics | CFC | SEM or range | CS | SEM or range |
|---|---|---|---|---|
| Age, y | 15.1 | 6-35 | 14.5 | 6-31 |
| Number of nevi on back | 47.8 | 14 | 8.1 | 1.8 |
| Phototype I | 6.0 | n/a* | n/a | n/a |
| Phototype II | 77.0 | 17.3 | 2.4 | 0.4 |
| Phototype III | 53.7 | 31.5 | 9.2 | 2.6 |
| Phototype IV | 16.0 | 5.0 | 10.3 | 3.7 |
| Phototype V | 15.0 | n/a* | 35.0 | n/a* |
| Phototype VI | 4.0 | n/a* | 9.0 | n/a* |
| Number of nevi on face | 24.3 | 7.3 | 4.0 | 0.8 |

*CFC*, Cardiofaciocutaneous syndrome; *CS*, Costello syndrome; *n/a*, not applicable; *SEM*, standard error of the mean.
*Only 1 individual; therefore, SEM is not applicable.

adolescents in the United States.[9] The average number of nevi on the face was also increased in CFC (CFC: 24.3 [SEM, 7.3]; CS: 4.0 [SEM, 0.8]; $P = .001$). The number of nevi was higher for patients with older age (beta estimate, 1.8; 95% confidence interval, 0.3-3.3; $P = .02$). Moreover, the number of nevi was significantly higher for phototypes I through III in CFC compared with CS but not for phototypes IV through VI ($P = .01$). There were no significant differences in painful sunburns ($P > .99$), sunbathing habits ($P > .99$), or hours spent outdoors between CFC and CS patients ($P = .48$).

BRAF p.V600E is a well-known somatic driver of nevogenesis. This study expands our knowledge of germline regulators of nevus count by suggesting that germline mutations in *BRAF*, *MAP2K1*, and *MAP2K2*, but not the upstream core component of the RAS pathway *HRAS*, predispose to and influence the number of nevi. Moreover, increased numbers of nevi, especially in individuals with phototypes I through III in CFC, suggest that ultraviolet (UV) radiation may enhance the effects of the germline mutations in the downstream components of the RAS pathway on nevogenesis. The results increase our knowledge of the genetic background and development of nevi, the potential precursors of melanoma. Although future studies are warranted to determine whether the risk of melanoma is increased in CFC, protection from UV radiation and regular skin examinations are appropriate for individuals with CFC.

We are grateful for the patients and families who participated in this study and Negar Foolad and Jed Smith for assistance with the study.

*Maija Kiuru, MD, PhD,[a,b] Jennifer Urban, MD,[a] Guannan Zhu, MD, PhD,[a,c] Iryna Rybak, BA,[a] Jessica R. Terrell, BA,[a] Lihong Qi, MS, PhD,[d] John D. McPherson, PhD,[e] Ashfaq A. Marghoob, MD,[f] and Katherine A. Rauen, MD, PhD[g]*

*From the Department of Dermatology, University of California, Davis, Sacramento[a]; Department of Pathology and Laboratory Medicine, University of California, Davis, Sacramento[b]; Department of Dermatology, Xijing Hospital, Fourth Military Medical University, Xi'an, Shaanxi, China[c]; Department of Public Health Sciences, University of California, Davis, Sacramento[d]; Department of Biochemistry and Molecular Medicine, University of California, Davis, Sacramento[e]; Dermatology Service, Memorial Sloan Kettering Cancer Center, New York[f]; and Department of Pediatrics, University of California, Davis, Sacramento.[g]*

*Funding sources: Supported by the Dermatology Foundation, through a Career Development*

*Award in Dermatopathology (to Dr Kiuru), and the National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, through grant no. K23AR074530 (to Dr Kiuru) and grant no. R01AR062165 (to Dr Rauen).*

*Conflicts of interest: None disclosed.*

*Part of this project was presented at the Society of Investigative Dermatology Annual Meeting, Chicago, IL, May 8-11, 2019.*

*IRB approval status: Reviewed and approved by University of California Davis IRB (960347).*

*Reprints not available from the authors.*

*Correspondence to: Maija Kiuru, MD, PhD, Department of Dermatology, University of California, Davis, 3301 C St, Ste 1450, Sacramento, CA 95816*

*E-mail: mkiuru@ucdavis.edu*

**REFERENCES**

1. Gandini S, Sera F, Cattaruzza MS, et al. Meta-analysis of risk factors for cutaneous melanoma: I. common and atypical naevi. *Eur J Cancer*. 2005;41:28-44.
2. Cancer Genome Atlas Network. Genomic classification of cutaneous melanoma. *Cell*. 2015;161:1681-1696.
3. Rauen KA. The RASopathies. *Annu Rev Genomics Hum Genet*. 2013;14:355-369.
4. Siegel DH, McKenzie J, Frieden IJ, Rauen KA. Dermatological findings in 61 mutation-positive individuals with cardiofaciocutaneous syndrome. *Br J Dermatol*. 2011;164:521-529.
5. Niihori T, Aoki Y, Narumi Y, et al. Germline KRAS and BRAF mutations in cardio-facio-cutaneous syndrome. *Nat Genet*. 2006;38:294-296.
6. Rodriguez-Viciana P, Tetsu O, Tidyman WE, et al. Germline mutations in genes within the MAPK pathway cause cardio-facio-cutaneous syndrome. *Science*. 2006;311:1287-1290.
7. Aoki Y, Niihori T, Kawame H, et al. Germline mutations in HRAS proto-oncogene cause Costello syndrome. *Nat Genet*. 2005;37:1038-1040.
8. Urban J, Qi L, Zhao H, Rybak I, Rauen KA, Kiuru M. Comparison of hair manifestations in cardio-facio-cutaneous and Costello syndromes highlights the influence of the RAS pathway on hair growth. *J Eur Acad Dermatol Venereol*. 2020. https://doi.org/10.1111/jdv.16082. Accessed February 12, 2020.
9. Oliveria SA, Satagopan JM, Geller AC, et al. Study of Nevi in Children (SONIC): baseline findings and predictors of nevus count. *Am J Epidemiol*. 2009;169:41-53.

https://doi.org/10.1016/j.jaad.2020.01.038