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# RAS pathway influences the number of melanocytic nevi in Cardio-facio-cutaneous and costello syndromes

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## Keywords

melanocytic nevus; melanocyte; RASopathy; RAS pathway; *BRAF*; *MAP2K1*; *MAP2K2*; *HRAS*; mutation; gene; nevogenesis; germline

Dear Editor, the number of melanocytic nevi is one of the strongest risk factors for melanoma,[1] yet the reasons for the interpersonal variability in their 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.

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To determine how the number of melanocytic nevi is influenced by the RAS pathway, we analyzed the numbers of nevi in Cardio-facio-cutaneous 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] while CS results from mutations in an upstream core component of the pathway, *HRAS* (Figure 1).[7]

The Institutional Review Board at 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). The photographs were examined for the number of nevi by two 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 two 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 with CS 14.5 years (range 6–31 years)[8]. The majority of individuals with CFC reported a *BRAF* mutation (*BRAF* in 13/16 or 81.3%, *MAP2K1* in 1/16 or 6.3%, *MAP2K2* in 1/16 or 6.3%, unknown 2/16 or 12.5%) and individuals with CS an *HRAS* mutation (p.G12S in 16/25 or 64.0%, p.G12C in 2/25 or 8.0%, and p.G12A, p.G13C, p.G13D, p.A146V, and p.K117R in in 1/25 or 4.0% each, unknown 2/25 or 6.3%)[8].

A marked difference was noted in the number of nevi in CFC versus CS (Figure 2, Table 1). The average number of nevi on the back was 47.8 in CFC (SEM 14.0) and 8.1 in CS (SEM 1.8, p=0.002). The number of nevi in CS corresponds to published population-based data of 8.4 nevi on average on the back of children and adolescents in the United States.[9] The average number of nevi on the face was also increased in CFC (24.3 in CFC, SEM 7.3, vs 4.0 in CS, SEM 0.8, p=0.001). The number of nevi was higher for patients with older age (beta estimate = 1.8, 95% I 0.3 – 3.3, p = 0.02). Moreover, the number of nevi was significantly higher for phototypes I-III in CFC compared to CS but not for phototypes IV-VI (p = 0.01). There were no significant differences in painful sunburns (p=1.0), sun bathing habits (p=1.0), or hours spent outdoors between CFC and CS patients (p=0.48).

BRAF p.V600E is a well-known somatic driver of nevogenesis. This study expands our knowledge on 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 phototype I-III in CFC suggest that 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 on the genetic background and development of nevi, the potential precursors of melanoma. While future studies are warranted to determine whether the risk of melanoma is increased in CFC, protection from UV radiation and regular skin exams are appropriate for individuals with CFC.

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## Abbreviations used

| | |
|---|---|
| **SEM** | standard error of mean |

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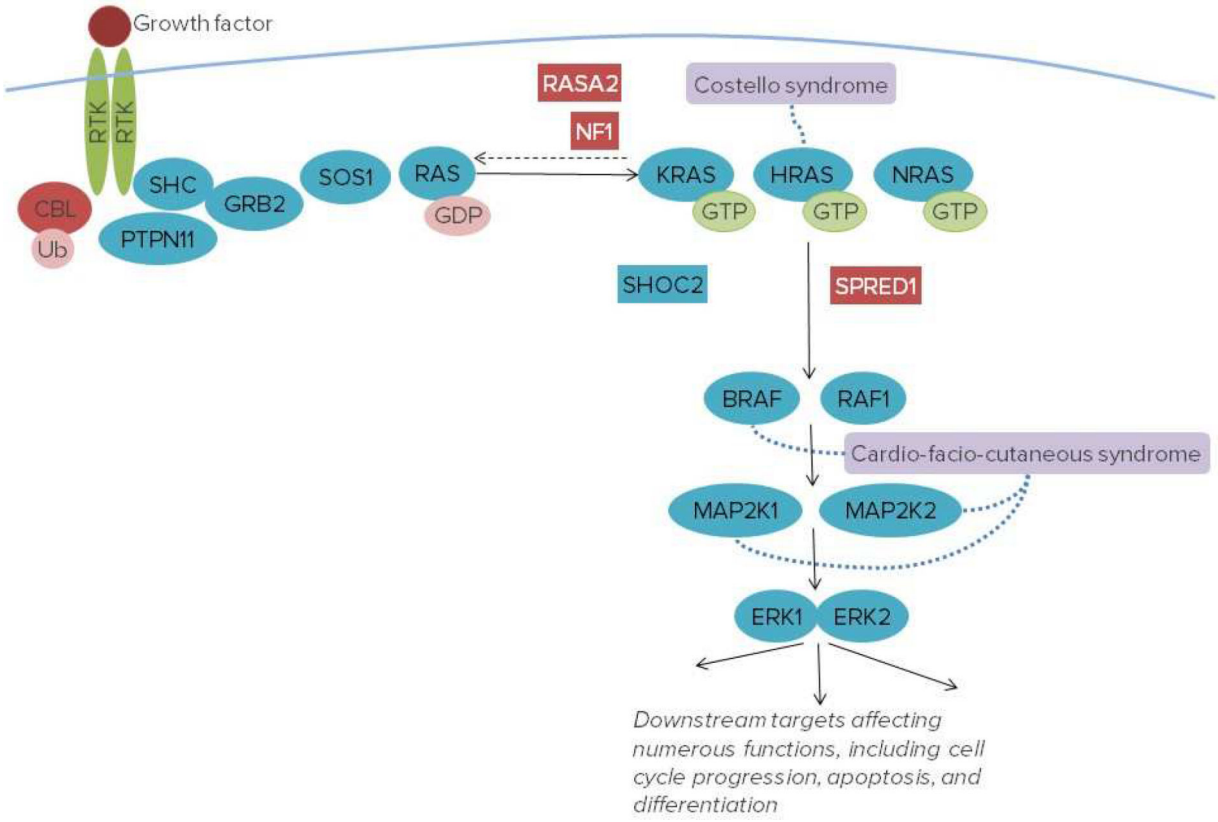


**Figure 1.**
The RAS pathway showing genes mutated in CFC and CS patients in this study.

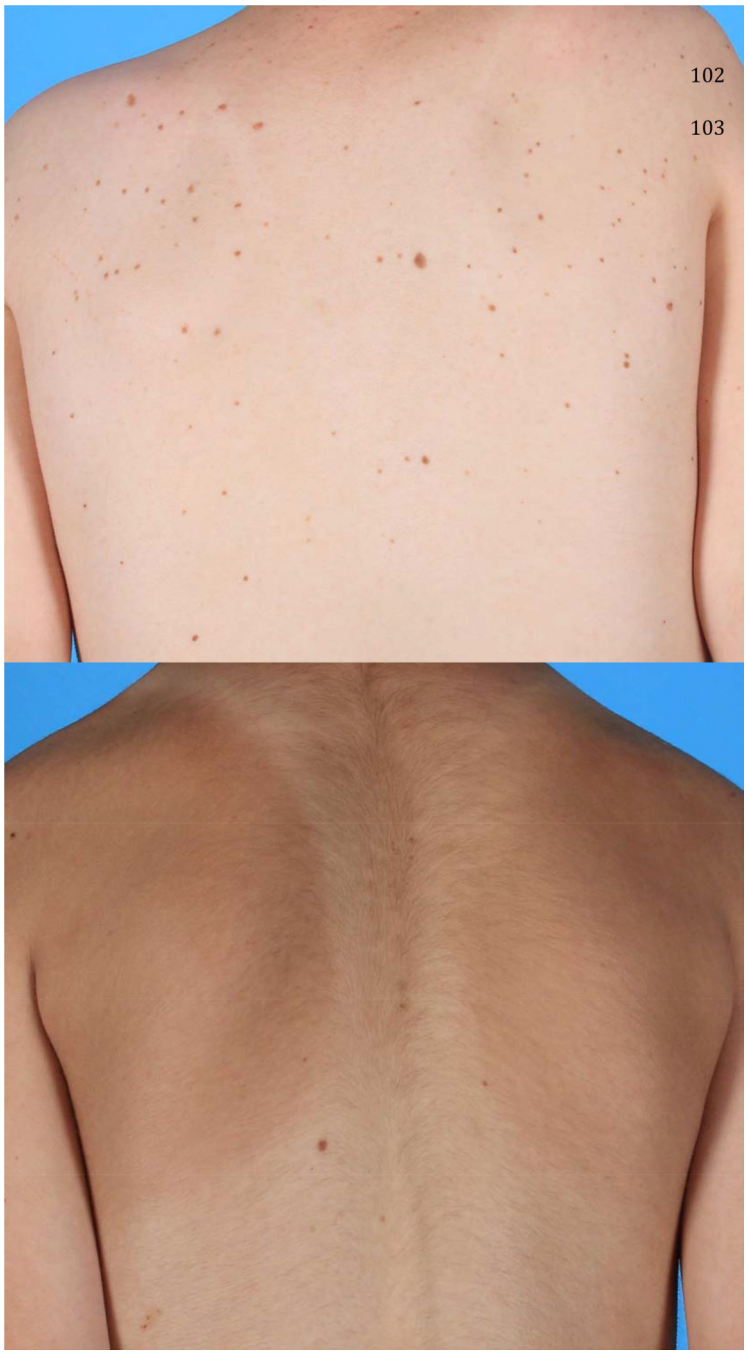


**Figure 2.**
Increase in the number of nevi in an individual with CFC (upper) compared with an individual with CS (lower). Both individuals are females between ages 22–23.

**Table 1.**

Number of nevi in CFC and CS.

| | CFC | SEM or range | CS | SEM or range |
|---|---|---|---|---|
| Age | 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[1] | 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[1] | 35.0 | n/a[1] |
| Phototype VI | 4.0 | n/a | 9.0 | n/a |
| Number of nevi on face | 24.3 | 7.3 | 4.0 | 0.8 |

[1] one individual only, therefore SEM not applicable