

A mosaic variant in *MAP2K1* is associated with giant naevus spilus-type congenital melanocytic naevus and melanoma development

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DEAR EDITOR, Giant congenital melanocytic naevi (CMN) arise primarily due to postzygotic mutations in *NRAS*, and are of clinical importance due to their increased risk of malignant transformation.¹ A subtype of large CMN, termed naevus spilus (NS)-type CMN, is identified by the presence of a patch that may have café-au-lait pigmentation and superimposed macular or papular lesions, which are demonstrably melanocytic naevi on histology. We present a patient who developed three melanomas within a NS-type CMN affecting the entire

left leg, where a pathogenic variant in the Ras signalling pathway gene *MAP2K1* was identified.²

A 43-year-old female presented with a superficial spreading malignant melanoma (SSMM) on the left medial thigh, with a Breslow thickness of 0.6 mm. A clinical decision for excision was made as it was distinct from other naevi on the leg. Two further melanomas were identified on the left lateral foot (Figure 1) and left lateral thigh, reported as lentiginous malignant melanoma (LMM), Breslow thickness of 0.3 mm and a LMM with complete regression of the dermal component, respectively. The unilateral presentation was not associated with background café-au-lait pigmentation; however, it was apparent that there were many more dark naevi on the affected limb compared with the rest of the patient's skin, suggesting cutaneous mosaicism.

Following patient consent, DNA was isolated from two of the melanomas and the NS-type CMN on the left thigh and analysed using targeted next-generation sequencing of a panel

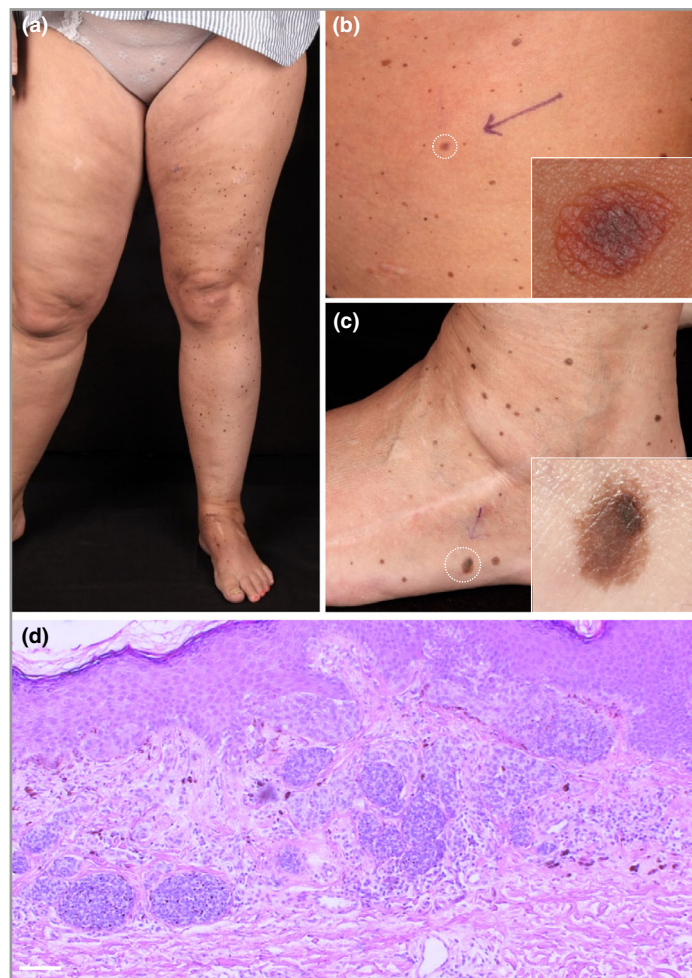


Figure 1 (a) Naevus spilus-type congenital melanocytic naevi involving the entire left leg and left suprapubic region, presenting as unilateral increased melanocytic naevi and melanoma. (b) Close-up of the superficial spreading malignant melanoma arising on the left thigh (indicated by the white dotted circle and inset image), within the confines of the NS-type congenital melanocytic naevi (CMN). (c) Close-up of another melanoma arising on the left lateral foot (indicated by white dotted circle and inset image), within the confines of the NS-type CMN. (d) Histology of the melanoma from the left thigh (haematoxylin and eosin, original magnification $\times 20$; white scale bar = 100 μm).

of pigmentation-related genes³ with a median on target fold coverage of > 1000 ×. A missense substitution at codon 203 in MAP2K1 (c.607G>A, p.E203K) was identified within both melanomas (medial left thigh and left lateral foot) and also within the background NS-type CMN. Allele loads were 7% in the SSMM, 2% in the LMM and 1% in the NS-type CMN. A second variant in MAP2K1 (c.308T>A, p.I103N) was also seen in the SSMM (7% allele load), but undetectable in the other melanoma and NS-type CMN. Targeted sequencing specifically excluded HRAS, NRAS and BRAF mutations in the NS-type CMN and melanomas.

NS-type CMN have previously been associated with specific mosaic variants in NRAS.^{1,2,4} Our patient differs phenotypically from prior cases and has many small, dark naevi on the skin of the affected limb with no apparent café-au-lait pigmentation. These naevi were not present at birth, and continue to develop. NS-type CMN are a clinically heterogeneous entity, and our finding of a postzygotic mutation in MAP2K1 adds to known existing drivers such as NRAS.⁴ The MAP2K1 E203K variant lies within the protein kinase domain of the MAP2K1 protein. This results in a gain of function at the protein level; E203K-mutated melanoma cell lines demonstrate constitutive phosphorylation of extracellular signal-regulated kinase, a downstream kinase in the Ras signalling pathway.⁵ Importantly, similar mutations in the germline give rise to cardiofaciocutaneous syndrome, which has been associated with increased numbers of melanocytic naevi, adding support for the pathogenicity of this variant.⁶ Furthermore, MAP2K1 mutations have been found in up to 6% of cases in a series of melanoma.⁵ Mosaic MAP2K1 variants have recently been described as a cause of arteriovenous malformations,³ but not previously in melanocytic lesions. Taken together, our findings suggest that our patient's NS-type CMN is driven by a postzygotic mutation in MAP2K1, predisposing to development of melanoma within the lesion. It is of interest that a second pathogenic variant in MAP2K1 (p.I103N) was detected in one melanoma at an identical allele load. It hints at the possibility that biallelic mutations in MAP2K1 are important to initiate melanoma formation in this birthmark. It would be of interest to determine if loss of heterozygosity of MAP2K1 has occurred specifically in melanoma cells in this patient's remaining melanomas; however, technical issues relating to working with paraffin-embedded tissue prevent this from being demonstrated unequivocally. Our findings highlight the clinical and genetic heterogeneity in NS-type CMN. These data add evidence to the central role of Ras signalling in CMN and melanoma development, and the need for long-term follow-up of such patients.

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Partner bereavement and risk of chronic urticaria, alopecia areata and vitiligo: cohort studies in the UK and Denmark

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DEAR EDITOR, The pathogenesis of skin diseases are not fully understood. Psychological stress has been proposed to be associated with skin diseases, but the epidemiological evidence is limited.^{1,2} We have recently reported the associations between partner bereavement (an extreme life stressor) and psoriasis, atopic eczema and melanoma.^{3,4} In this study, we further