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Clinical Consequences of Cancer-related RAS Signaling Pathway Beyond Malignancy

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ABSTRACT

Aim: Mosaic variants in oncogenic signaling pathways, particularly the Rat Sarcoma/Mitogen-Activated Protein Kinase *(RAS/*MAPK) cascade, are increasingly recognized causes of non-malignant developmental disorders presenting with segmental cutaneous manifestations.

Methods: We evaluated patients carrying somatic mosaic variants in the Kirsten *RAS* Viral Oncogene Homolog, Neurofibromin 1, Fibroblast Growth Factor Receptor 3, and Neuroblastoma RAS Viral Oncogene Homolog genes. Molecular analyses were performed with emphasis on tissue-specific sequencing to detect low-level mosaicism.

Results: The reported cases demonstrate the broad phenotypic spectrum of mosaic *RAS/*MAPK-related disorders. Clinical severity was shown to depend on both the type of variant and the extent of mosaic distribution. Importantly, several low-frequency variants were detectable only in affected tissue, highlighting the diagnostic value of tissue-specific molecular testing.

Conclusion: Current American College of Medical Genetics and Genomics/Association for Molecular Pathology guidelines for germline and cancer-associated variants are insufficient to classify somatic mosaic variants underlying cutaneous disorders. Our findings emphasize the need to reshape diagnostic approaches and variant classification strategies for mosaic *RAS/*MAPK-related dermatologic conditions.

Keywords: Skin, somatic, RAS pathway, mosaic, postzygotic

Introduction

The Rat Sarcoma/Mitogen-activated Protein Kinase *(RAS/*MAPK) signaling pathway plays a central role in regulating fundamental biological processes such as cell growth, proliferation, and differentiation. Germline pathogenic variants in genes of this pathway are responsible for a group of neurocutaneous developmental disorders collectively known as *RAS opathies*. In recent years, postzygotic (mosaic) activating variants in genes such as Harvey *RAS* Viral Oncogene Homolog (*HRAS),* Kirsten *RAS* viral oncogene homolog *(KRAS),* Neuroblastoma *RAS* viral oncogene homolog *(NRAS)*, and Protein Tyrosine Phosphatase Non-receptor Type 11 (*PTPN11)* have also been increasingly recognized as causative of mosaic forms of *RASopathies*, which represent phenotypically distinct and increasingly well-defined clinical entities [1]. These disorders typically present in the neonatal or early childhood period with cutaneous, vascular, skeletal, and neurological anomalies, accompanied by segmental proliferative lesions and an increased risk of malignancy. Due to the mosaic nature of the variants, clinical findings are frequently asymmetric, segmental, or localized, and may be missed if genetic testing is limited to peripheral blood samples.

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In this study, we present a series of patients harboring mosaic pathogenic variants in genes of the *RAS*/MAPK signaling pathway, and we emphasize the complementary role of genetic and dermatologic evaluation in the recognition of mosaic signaling disorders.

Methods

All procedures performed in this study were carried out in accordance with the ethical standards stated in the World Medical Association Declaration of Helsinki. Ethics committee approval for the study was received from the Scientific Research Evaluation and Ethics Committee of Ankara Etlik City Hospital on (decision no: AEŞH-BADEK-2024-757, date: 28.08.2024). This study is descriptive in nature, and no statistical analysis was performed because the dataset did not require comparative or inferential evaluation.

Five patients who presented to Ankara Etlik City Hospital were included in the study. Written informed consent was obtained from all patients or their legal guardians. In retrospectively evaluated clinical exome sequencing, the following kits were used. For G23-25265, G23-9663, and BSH1 patients' *genomic* deoxyribonucleic acid (DNA) extracted from affected skin tissue samples was used for library preparation with the Sophia Clinical Exome Solution V3 capture kit (SOPHiA Genetics SA, Switzerland) and was sequenced on the MiSeq platform (Illumina Inc., CA).

For patient G24-25268, DNA extracted from the patient's skin tissue sample was analyzed by next-generation sequencing (NGS) on the Seq Genomize V8.2.3 platform (Roche), and library preparation was performed using the KAPA HyperCap Custom kit. The corresponding Binary Alignment/Map file alignments, visualized with Integrative Genomics Viewer, are provided in the Supplementary Material.

Ribonucleic acid was isolated from the fibroblast tissue of patient G24-7460 and quantified using a Qubit fluorometer. Libraries were prepared with the Archer® Comprehensive Thyroid & Lung Kit, indexed, and sequenced on an NGS platform.

Results

Patients

G23-25265

An 8-year-old girl was referred for evaluation of congenital focal alopecia of the scalp and linear cutaneous hyperpigmentation. She was the fifth child of parents related at the third degree. Prenatal history was unremarkable, and neurodevelopment was age-appropriate. Vision and hearing assessments, echocardiography, brain magnetic resonance imaging (MRI), and abdominal ultrasound were within normal limits. Academic performance was reported as good. Anthropometric measurements were as follows: weight, 30 kg [standard deviation score (SDS): +0.48]; height, 121 cm (SDS: -1.57); and head circumference, 53 cm (SDS: +0.63). Physical examination revealed a relative nevus sebaceous on the scalp (Figure 1a), macrocephaly, sparse, lusterless hair with patchy alopecia, and dysmorphic features including coarse facial appearance, high forehead, mild synophrys, broad nasal root, full lips (Figure 1b), short neck, low posterior hairline, and hypopigmented macules along Blaschko's lines (Figure 1c). Conventional karyotyping and chromosomal microarray were normal. Because of pigmentary mosaicism and dysmorphic features, NGS of affected skin tissue was performed. A somatic *KRAS* (NM_004985.5) variant, c.26T>G; p.(Val9Gly), was detected [Variant Allele Frequency (VAF) 13; read depth 56]. According to American College of Medical Genetics and Genomics/ Association for Molecular Pathology (ACMG/AMP) guidelines, this variant was classified as likely pathogenic based on PM1, PM2, PP2, and PP3.

G24-25268

A 34-year-old woman was referred for evaluation of multiple neurofibromas localized to the back. Histopathological examination confirmed the diagnosis of neurofibroma, and the lesions were reported to have developed postnatally. Aside from cutaneous neurofibromas, she did not meet any other diagnostic criteria for Neurofibromin type 1 *(NF1)*. NGS of peripheral blood revealed no pathogenic variants in the *NF1 gene*. However, because of a segmental distribution and the absence of systemic involvement, mosaic *NF1* was suspected. Targeted NGS of affected skin tissue identified a somatic *NF1* variant: NM_001042492.3:c.7797_7806del, p.(Glu2600PhefsTer21), with a VAF consistent with mosaicism (VAF 8.23%; read depth 243). According to ACMG/AMP guidelines, this frameshift deletion was classified as likely pathogenic based on pathogenic very strong 1 and PM2.

G23-9663

A 4-year-old boy was referred for evaluation of hyperpigmented skin lesions distributed in a linear pattern on the neck, trunk, and inguinal region, accompanied by pruritus. The lesions began to appear around the fourth month of life and progressively spread. Prenatal and perinatal histories were unremarkable; he was born at term by cesarean section, weighing 3350 g. There was no parental consanguinity, and neurodevelopmental milestones were normal. At presentation, anthropometric measurements were: weight 17 kg (SDS: -0.53), height 104 cm (SDS: -1.16), and head circumference 51 cm (SDS: -0.35). Physical examination revealed a widow's peak; wavy, woolly hair; downslanted palpebral fissures; a prominent lower lip; and papillomatous lesions around the perioral and periorbital areas. Additionally, hyperkeratotic verrucous plaques were noted in the cervical and axillary regions (Figures 1d, 1e), and linear and whorled hyperpigmented patches or plaques following Blaschko's lines were observed over the trunk (Figure 1f) and extremities (Figure 1g). Abdominal ultrasonography was unremarkable. Histopathological examination of a skin biopsy demonstrated basket-weave hyperkeratosis, papillomatosis, and focal vacuolization in the basal layer of

the epidermis. Targeted NGS of the affected tissue revealed a somatic Fibroblast Growth Factor Receptor 3 (*FGFR3)* variant: NM_000142.5:c.742C>T; p.(Arg248Cys) (VAF 9%; read depth 165). This variant is classified as pathogenic according to the ACMG guidelines (PS3, PS4, PM1, PM2, PP3, PP5).

G24-7460

A 4-year-old boy with a history of congenital giant nevus was referred for genetic evaluation. He was the child of parents described as non-consanguineous but with a known fourth-degree familial relationship. Prenatal and perinatal histories were unremarkable; he was born at 41+3 weeks' gestation via normal spontaneous vaginal delivery, with a birth weight of 3,600 g. Neurodevelopmental milestones were appropriate for age. At the time of examination, his weight, height, and head circumference were 13 kg, 94 cm, and 48 cm, respectively. Physical examination revealed lateral thinning of the eyebrowsand numerous melanocytic nevi with hairs of various lengths throughout the body, including a giant congenital nevus on the back (Figures 1h, 1i). In addition, bilateral pes planus and prominent heels were noted. Audiological and ophthalmological assessments, as well as cranial MRI and abdominal ultrasonography, were within normal limits. NGS of affected skin tissue identified a somatic variant in the *NRAS gene* (NM_002524.5:c.182A>G; p.Gln61Arg), consistent with a molecular diagnosis of congenital melanocytic nevus syndrome (CMNS) (VAF 25%, read depth: 300). This variant is classified as pathogenic according to ACMG guidelines (PS3, PS4, PM1, PM2, PP2, PP3).

BSH1

An 8-month-old female patient was born at 35 weeks' gestation with a birth weight of 2620 g. She was referred for dysmorphic facial features and skin lesions. Her parents were consanguineous. Physical examination revealed macrocephaly; hypertelorism; eyelid coloboma; bilateral eyelid hypoplasia (Figure 1j); protruding conjunctiva; sparse hair, eyebrows, and eyelashes; macroglossia; and hypopigmented linear verrucous plaques along Blaschko's lines on the chin and back (Figure 1k). Her weight was 4 kg [-5.9 standard deviation (SD)] and her length was 60 cm (-4.4 SD). Echocardiography demonstrated coarctation of the aorta and hypoplasia of the transverse aortic arch and isthmus. Ophthalmological examination of the left eye revealed a lid lipodermoid and aniridia. Abdominal ultrasonography and hearing screening were normal. Chromosome analysis revealed a 46,XX karyotype. A pathogenic *KRAS* variant, NM_004985.5:c.35G>A (p.Gly12Asp) (rs121913529) (VAF 31%, read depth 163), was identified by a *RASopathy* gene panel performed on a skin biopsy. This variant is classified as pathogenic according to ACMG guidelines (PS3, PS4, PM1, PM2, PP2, PP3). The patient died at 10 months of age due to respiratory distress and sepsis.

Table 1 presents the detected somatic mosaic variants in the study cohort, together with their tissue distribution, variant allele frequencies, and sequencing depths.

Discussion

The cases presented in this series illustrate the expanding spectrum and diagnostic complexity of mosaic disorders involving oncogenic signaling pathways, particularly the *RAS*/MAPK and *PI3K/AKT/mTOR* cascades. Although these pathways have traditionally been associated with cancer pathogenesis, dysregulation of these pathways due to postzygotic activating variants has increasingly been implicated in non-malignant developmental disorders with highly variable and often segmental phenotypic manifestations. Our findings underscore the diagnostic value of detailed dermatological assessment for the early recognition of mosaic signaling disorders, particularly in individuals with localized pigmentary or proliferative cutaneous anomalies. Furthermore, the detection of low-level somatic variants in affected tissue, undetectable in peripheral blood, highlights the necessity of tissue-specific molecular testing in the diagnostic evaluation of suspected mosaic phenotypes. These cases, which present both classical and atypical clinical features, contribute to the growing body of evidence bridging cancer biology and developmental genetics, and emphasize the importance of interdisciplinary collaboration in the management of such patients.

Our two patients with mosaic *KRAS* variants highlight the wide phenotypic spectrum of epidermal nevus syndromes. G23-25265, carrying the rare p.(Val9Gly) variant, presented with a scalp lesion that was clinically suggestive of nevus sebaceus, which dermatological evaluation described as more consistent with scarring alopecia, along with patchy alopecia, hypopigmented macules along Blaschko's lines, and dysmorphic features, without neurological or systemic involvement. Histopathological confirmation could not be performed; therefore, the exact classification of the lesion remains uncertain. The literature indicates that mosaic *KRAS* variants are not restricted to classical nevus sebaceus but can also present as linear or segmental keratinocytic epidermal nevi, pigmentary mosaicism, and occasionally mucosal involvement, supporting a broader phenotypic spectrum [2]. To the best of our knowledge, the p.(Val9Gly) variant has not previously been reported in association with this presentation, raising the possibility of a novel genotype-phenotype correlation at the milder end of the spectrum. In contrast, the BSH1 case supports previous reports of patients with Schimmelpenning-Feuerstein syndrome, in whom the p.Gly12Asp variant has been associated with multisystem involvement and a severe clinical course. Moreover, a relatively high mosaicism rate of 31% may account for the fatal outcome observed in this patient [2,3]. Taken together, these cases demonstrate that both the specific *KRAS* mutation and the extent of mosaic distribution are critical determinants of clinical severity, ranging from isolated cutaneous or dysmorphic findings to life-threatening multisystem disease.

The clinical and molecular findings of patient G24-25268 are consistent with a diagnosis of segmental neurofibromin (also referred to as mosaic *NF1*). According to current estimates, approximately 10% of patients with *NF1* have the mosaic form of the disease [2]. The patient presented with multiple

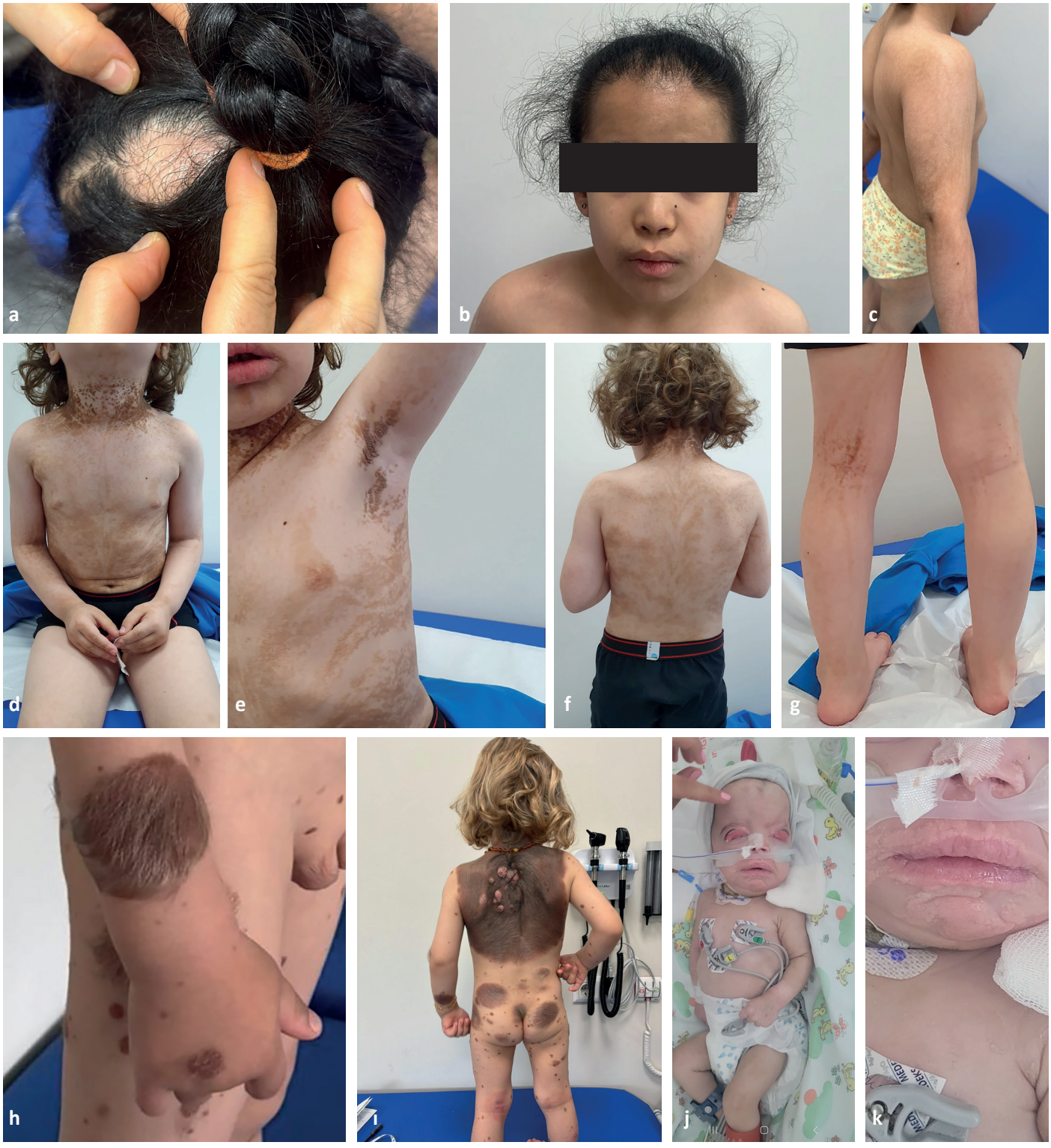

Figure 1. Patient photographs illustrating the phenotypic spectrum. **(a)** Patchy alopecia on the scalp **(b)** coarse facial features with a broad forehead, subtle synophrys, wide nasal bridge, and prominent lips **(c)** linear hypopigmented macules along Blaschko's lines on the right arm **(d)** linear blaskoid hyperpigmented verrucous plaques surrounding the neck and **(e)** axillary region and linear swirling hyperpigmented patches and plaques following Blaschko's lines on the anterior trunk, **(f)** back and **(g)** extremities **(h-i)** multiple melanocytic nevi of varying sizes with hypertrichosis on the right arm and back **(j)** macrocephaly, hypertelorism, eyelid coloboma, bilateral eyelid hypoplasia, sparse scalp hair, sparse eyebrows and eyelashes, macroglossia, and **(k)** hypopigmented linear verrucous plaques following Blaschko's lines on the chin, perioral region and around the nose

Table 1. Somatic mosaic variants identified in the study cohort, indicating the affected genes, variant type, tissue distribution, VAF, and coverage depth. Na: not applicable

Patient no	*Gene*	Variant	Affected tissue	Blood	VAF	Depth
G23-25265	*KRAS*	c.26T>G; p.(Val9Gly)	+	-	13%	56
G24-25268	*NF1*	c.7797_7806del, p.(Glu2600PhefsTer21)	+	-	8.2%	243
G23-9663	*FGFR3*	c.742C>T; p.(Arg248Cys)	+	NA	9%	163
G24-7460	*NRAS*	c.182A>G; p.(Gln61Arg)	+	NA	25%	300
BSH1	*KRAS*	c.35G>A (p.Gly12Asp)	+	NA	31%	163

VAF: Variant allele frequency, *KRAS:* Kirsten Rat Sarcoma Viral Oncogene Homolog, *NF1*: Neurofibromin Type 1, *FGFR3*: Fibroblast Growth Factor Receptor 3, *NRAS*: Neuroblastoma Rat Sarcoma Viral Oncogene Homolog

neurofibromas localized exclusively to the back and did not meet the National Institutes of Health diagnostic criteria for generalized *NF1*. The absence of systemic involvement and the postnatal onset of the lesions supported the suspicion of mosaicism. Targeted NGS of affected skin tissue revealed a somatic *NF1* frameshift variant—c.7797_7806del, p.(Glu2600PhefsTer21)—with a VAF of 8.23%, consistent with a mosaic pattern. This novel variant, not previously reported, was not detected in peripheral blood, further supporting its somatic origin. There are currently no specific follow-up guidelines for mosaic *NF1*. Based on previous reports indicating a 13% risk of malignancy in patients with mosaic *NF1* [2], the patient was counseled accordingly and scheduled for regular follow-up.

The *FGFR3* p.(Arg248Cys) hotspot mutation has been consistently reported as a pathogenic variant underlying mosaic epidermal nevus syndrome [4]. In some patients, this mutation extended beyond the epidermis into the oral mucosa or hematopoietic cells, suggesting an early embryonic mutational event [5]. In our patient, however, the mutation was confined to a nevus sebaceus on the scalp and to areas of hypopigmentation along Blaschko's lines, with no extracutaneous manifestations. The relatively low mutant allele frequency (~9-13%) further supports limited tissue involvement, which may account for the mild phenotype. While constitutional *Arg248Cys* mutations cause thanatophoric dysplasia, a typically lethal skeletal dysplasia [6], mosaic forms result in non-lethal presentations with variable expressivity. These observations highlight the wide phenotypic spectrum of *FGFR3* mosaicism and emphasize the need for careful dermatologic examination and tissue-specific molecular testing in suspected epidermal nevus syndromes. Even in the absence of systemic involvement, long-term surveillance is advisable, as extracutaneous features and rare complications have been described in previously reported cases [4,7].

In G24-7460, targeted sequencing of affected skin tissue identified the pathogenic hotspot *NRAS* p.(Gln61Arg), a recurrent postzygotic activating mutation well documented in CMNS and other mosaic *RASopathies* [8]. Together with p.Gln61Lys and p.Gly13Arg, this variant has been described as one of the most frequent drivers of large or multiple congenital melanocytic nevi and represents a prototypical example of somatic mosaicism [9]. The mutant allele frequency in our case (25%) was consistent with a mosaic state, as previously reported in similar patients [10]. Although extracutaneous features such as neurocutaneous melanosis, seizures, and structural central nervous system malformations have been described in association with CMNS [11], our patient exhibited only cutaneous findings, further highlighting the phenotypic variability of *NRAS*-driven mosaic disorders. The additional findings of pes planus and prominent heels may be incidental; however, given the pleiotropic effects of *RAS*/MAPK signaling, a contributory effect cannot be entirely excluded. Unlike some previously reported mosaic *RASopathy* patients in whom hypophosphatemic rickets has been documented [12], no biochemical evidence of hypophosphatemia was observed in our patient. However, because of the acute risk of developing rickets, he was placed under close clinical follow-up. Overall, our findings are consistent with previous reports and reinforce the concept that *NRAS* mosaicism underlies a clinically heterogeneous spectrum, emphasizing the importance of detailed dermatological assessment, tissue-specific molecular testing, and longitudinal surveillance in children presenting with extensive congenital melanocytic nevi.

There are currently no ACMG/AMP guidelines specifically developed for the classification of somatic mosaic variants associated with non-malignant cutaneous lesions, such as epidermal nevus syndromes or segmental neurofibromatosis. The widely adopted 2015 ACMG/AMP recommendations were primarily designed to evaluate germline variants, whereas the 2017 AMP/ASCO/CAP guideline was directed toward interpreting somatic variants in malignancies [13,14]. Consequently, the interpretation of variants identified in non-malignant cutaneous mosaic disorders generally relies on the application of germline ACMG/AMP criteria with appropriate modifications. However, the applicability and weight of these criteria can vary in the mosaic context. For example, evidence such as *de novo* occurrence or *gene*-specific loss-of-function can support pathogenicity, but interpretation must take into account the somatic mosaic nature and restricted tissue distribution of the variant. Collectively, our findings emphasize the need for tailored classification frameworks for somatic mosaic variants in dermatologic disorders, bridging the gap between germline guidelines and cancer-focused recommendations. Moreover, the genetic characterization of somatic mosaic skin disorders related to the *RAS*/MAPK pathway has advanced the understanding of disease pathogenesis and paved the way for the development of new

therapeutic targets. Indeed, targeted therapies originally developed for cancers with *RAS*/MAPK pathway alterations (such as MAPK inhibitors) may also hold therapeutic promise in cutaneous mosaic disorders driven by the same pathway, and their potential use in this context deserves further exploration. The increasing number of reported cases is expected to contribute to refining clinical approaches and to shaping treatment strategies with translational potential.

Study Limitations

This study is limited by the inability to demonstrate the absence of variants in blood samples from some patients (e.g., because of death), the lack of functional validation, and the absence of specific ACMG/AMP guidelines tailored for cutaneous mosaic variants. These factors may affect the generalizability and interpretation of our findings.

Conclusion

Mosaic disorders involving oncogenic signaling pathways represent a dynamic interface between developmental genetics and cancer biology. The cases presented herein highlight the wide phenotypic variability of *RAS*/MAPK-related mosaic syndromes and underscore the essential role of dermatologic evaluation and tissue-specific molecular testing in their diagnosis. The identification of novel and low-level mosaic variants further expands the genotypic and phenotypic spectrum of these disorders. Establishing standardized criteria for the interpretation of somatic mosaic variants in non-malignant settings and exploring the translational potential of pathway-targeted therapies remain important future goals.

Ethics

Ethics Committee Approval: All procedures performed in this study were carried out in accordance with the ethical standards stated in the World Medical Association Declaration of Helsinki. Ethics committee approval for the study was received from the Scientific Research Evaluation and Ethics Committee of Ankara Etlik City Hospital on August 28, 2024 (decision no: Aeşh-BADEK-2024-757, date: 28.08.2024).

Informed Consent: Informed consent forms for publication were obtained from the adult patients and from the legal guardians of the pediatric patients.

Footnotes

Authorship Contributions

Concept: E.T., A.S., Design: E.T., A.S., M.G., Data Collection or Processing: E.T., A.B., A.K., A.B.D.A., E.K., E.K., İ.K., Analysis or Interpretation: E.T., A.S., A.B.D.A., E.K., M.G., Literature Search: E.T., A.B., M.G., Writing: E.T., M.G.

Conflict of Interest: No conflict of interest was declared by the authors.

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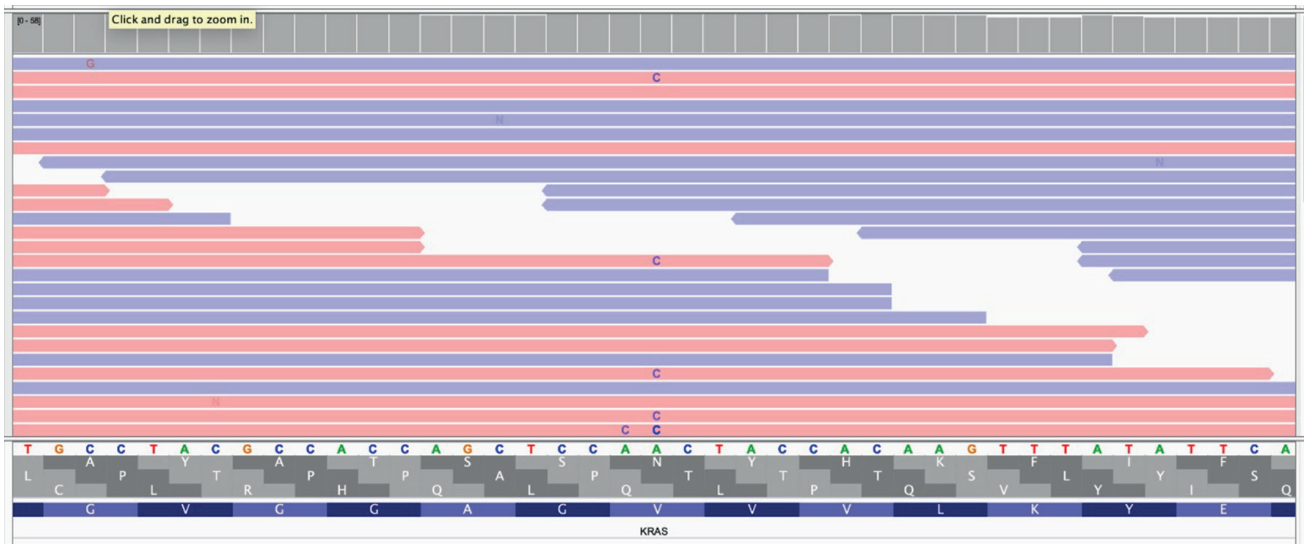
Supplementary Material



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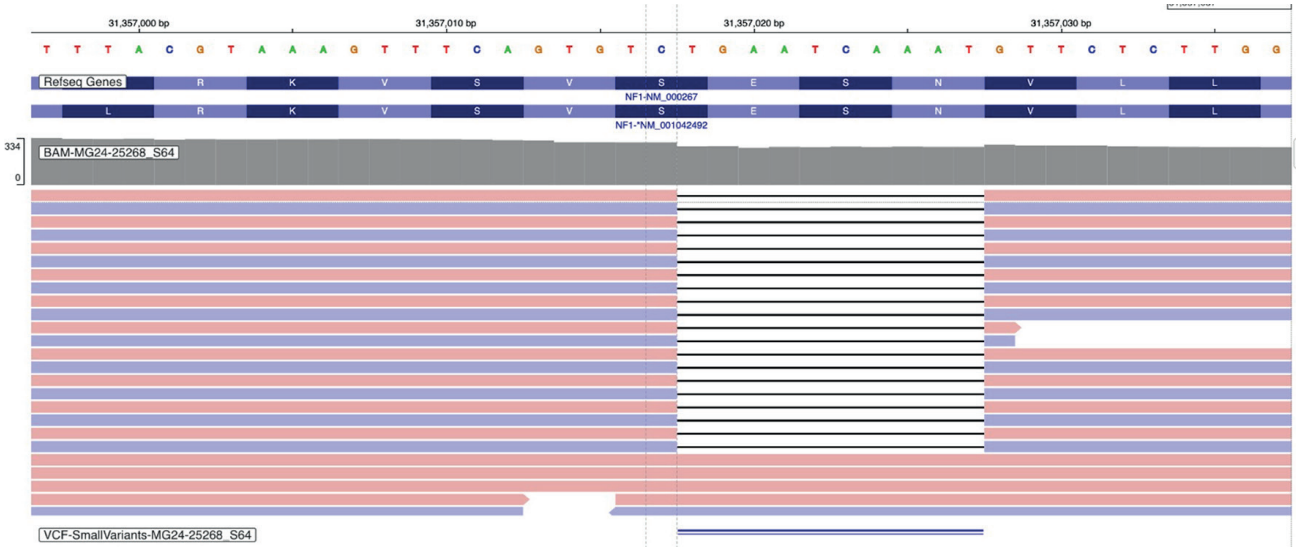
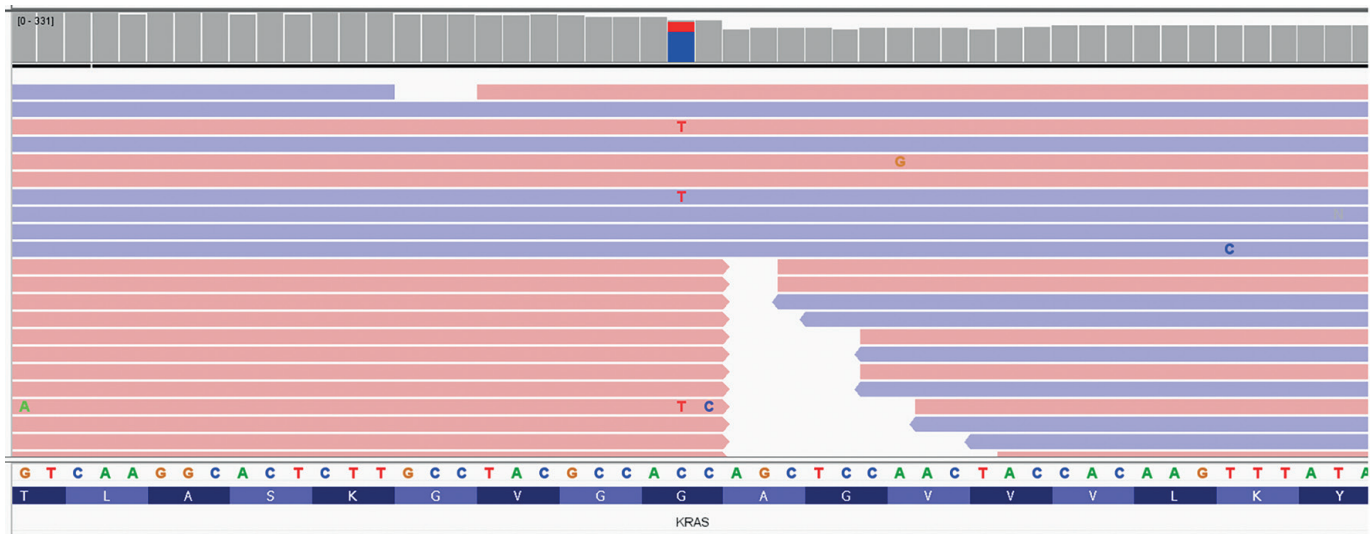


G24-25268

G23-9663

G24-7460



BSH1

Supplementary Material. Integrative Genomics Viewer (IGV) alignments showing the detected somatic variants, highlighted in red boxes: (a) *KRAS* c.26T>G; p.(Val9Gly), (b) *NF1* c.7797_7806del; p.(Glu2600PhefsTer21), (c) *FGFR3* c.742C>T; p.(Arg248Cys), (d) *NRAS* c.182A>G; p.(Gln61Arg), (e) *KRAS* c.35G>A; p.(Gly12Asp).

KRAS: Kirsten Rat Sarcoma Viral Oncogene Homolog, *NF1*: Neurofibromin Type 1, *FGFR3*: Fibroblast Growth Factor Receptor 3, *NRAS*: Neuroblastoma Rat Sarcoma Viral Oncogene Homolog