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CASE REPORT OPEN ACCESS

Mosaic *KRAS* Mutation in Schimmelpenning–Feuerstein–Mims Syndrome With Overlapping Oculoectodermal Syndrome and Encephalocraniocutaneous Lipomatosis Features

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ABSTRACT

We report a patient with clinically confirmed Schimmelpenning–Feuerstein–Mims (SFM) syndrome but many overlapping features with oculoectodermal syndrome (OES) and encephalocraniocutaneous lipomatosis (ECCL). Whole exome sequencing revealed a mosaic *KRAS* c.436G>A, p.(Ala146Thr) mutation, previously identified in three OES and ECCL patients. These findings corroborate the evidence of SFM syndrome being a mosaic *RAS*opathy, broaden the phenotypic spectrum of oculocutaneous mosaic *RAS*opathies, and indicate SFM syndrome as a continuum of the OES–ECCL disorder spectrum.

1 | Introduction

Mosaic mutations in *KRAS* and other *RAS*opathy genes can cause Schimmelpenning–Feuerstein–Mims (SFM) syndrome, oculoectodermal syndrome (OES), encephalocraniocutaneus lipomatosis (ECCL), and vascular malformations including asymmetric overgrowth [1]. SFM syndrome is a congenital neurocutaneous disorder characterized by craniofacial nevus sebaceus with extracutaneous ocular, cerebral, or skeletal defects [2]. Recently, somatic mutations in *HRAS*, *KRAS*, and *NRAS* have been identified in association with SFM syndrome [3, 4]. We report an adolescent with a nevus sebaceus covering part of the scalp and the right side of his head combined with other distinctive features for SFM syndrome but also for OES and ECCL. The patient was identified with a mosaic mutation of *KRAS* c.436G>A, p.(Ala146Thr) previously reported pathogenic for OES and ECCL in three patients [5, 6].

2 | Case Report

A full-term male was born via spontaneous delivery after an uneventful pregnancy despite the mother's gestational diabetes. He is the fourth child of nonconsanguineous parents. There

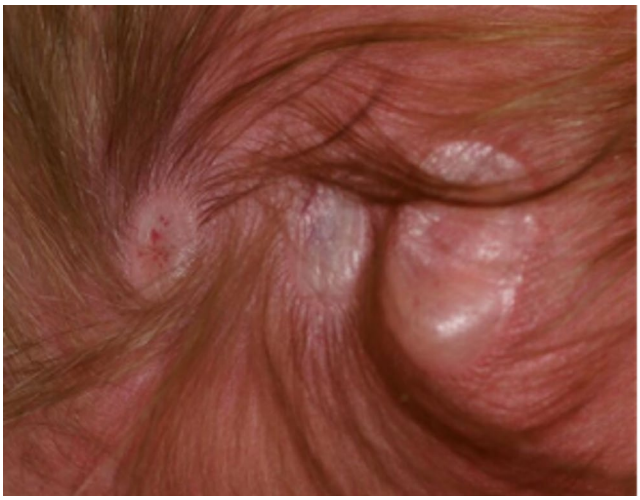

FIGURE 1 | Bullous vesicles at vertex at 2 days old.

was no family history of symptoms suggestive of SFM syndrome or dermatological diseases other than atopic dermatitis in the mother and hand eczema in the father. At birth, his physical examination revealed congenital bullae and vesicles with yellow fluid located at the vertex (Figure 1), an epibulbar tumor, and a right upper eyelid coloboma. A slightly elevated salmon-colored plaque extended from the right temporal region to the corner of the ipsilateral eye and the lower chin. Brain and abdominal ultrasound (US), brain magnetic resonance imaging (MRI), echocardiography, and neurological examinations were normal.

At 6 weeks of age, the bullae on the scalp were replaced by five focal alopecic plaques, raising clinical suspicion of aplasia cutis. This was confirmed later in puberty with the biopsies taken from the alopecic areas that supported a diagnosis of aplasia cutis with fibrosis and lack of skin appendages. A salmon-colored nevus sebaceus in the temporal area becoming slightly darker and more prominent toward puberty was clinically diagnosed but not histologically confirmed. The epibulbar tumor of the eye was excised, and histopathology revealed a corneal dermoid. Ophthalmological examination revealed right eye amblyopia but normal left eye vision.

At 4 years of age, the patient was diagnosed with type 1 diabetes and complained of right knee pain and right lower extremity swelling. X-rays revealed a lytic lesion on the proximal tibia, and MRI indicated a benign fibrotic cortical defect, suggesting a nonossifying fibroma. The swelling was diagnosed as lymphedema, which worsened, causing asymmetry and overgrowth (Figure 2). Lymphedema was treated with manual lymphatic drainage and compression garments.

At age 9 years, he was diagnosed with SFM syndrome in the context of marked linear and blaschkoid hyperpigmented patches on his back, neck, right upper, and lower extremities (which became visible at age 5 years) combined with the nevus sebaceus of his face (Figures 3 and 4), ocular, and skeletal abnormalities.

Brain and spine MRI showed several small intracranial and intraspinal lipomas which were not apparent on prior imaging. Blood tests were unremarkable including complete blood

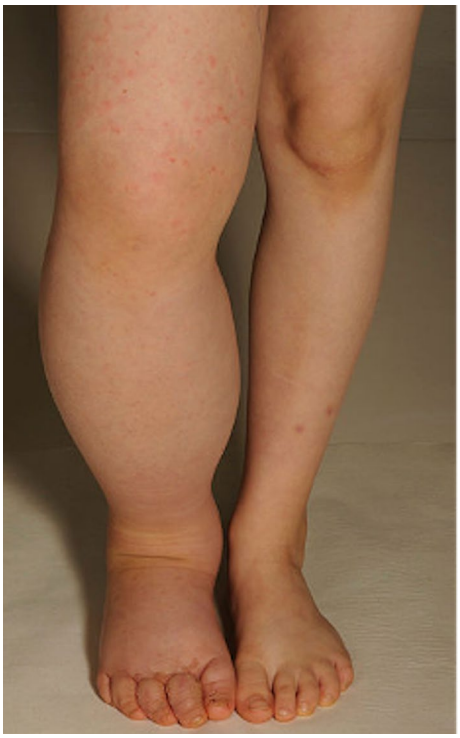

FIGURE 2 | Lymphedema of the right lower extremity at 9 years old.

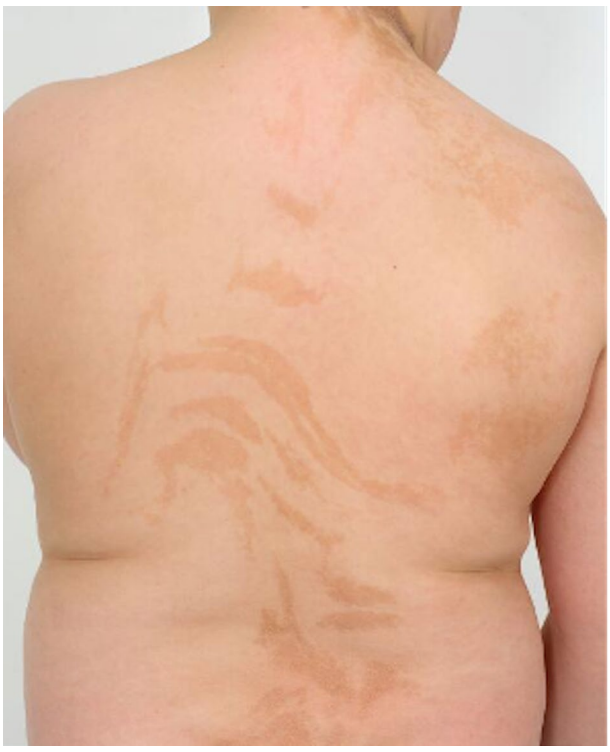

FIGURE 3 | Linear hyperpigmentated patches on the right side of the body at 9 years old.

count, thyroid function tests, 25-hydroxy-vitamin D_3, plasma and urinary levels of calcium and phosphorus. The right leg had varus deformity and computed tomography (CT) showed a healing bone fracture across the fibrotic cortical defect of the proximal right tibia. Bone mineral content and density were

FIGURE 4 | Nevus sebaceus of the right forehead at 14 years old.

normal without evidence of rickets on dual-energy x-ray absorptiometry studies. The varus deformity was treated with minimally invasive correcting osteotomy using a stabilizing external fixator. Lymph leakage was noted from the external fixator pins, the groin, scrotum, and toes, and a chylous diet was instituted.

Dynamic contrast-enhanced MR lymphangiography accompanied with CT demonstrated abnormal lymphatics resulting in lymphedema and lymphatic reflux on the right lower extremity, scrotum, right kidney and distal urethra, retroperitoneum, and lungs. Furthermore, a contrast-enhanced and dilated thoracic duct in the upper thorax raised suspicion of stenosis. At age 12 years, the adhesions from the superior thoracic duct were excised, and the junction of thoracic duct and left internal vein drained normally, with reduction in lower limb lymphedema. Three years later, three additional lymphaticovenous anastomoses were performed to improve volume reduction.

Comparative whole-exome sequencing (Blueprint Genetics) was performed at age 15 years of age on DNA isolated from the patient's affected and unaffected skin cells. In 33% of the affected cells a c.436G>A p.(Ala146Thr) variant was found in the *KRAS* (NM_004985.5), whereas the variant was absent in the unaffected cells. Bidirectional Sanger sequencing confirmed the finding of this mosaic variant. This *KRAS* mutation was classified as a likely pathogenic variant as the variant is extremely rare in control populations, and in silico predictions suggested pathogenicity. Furthermore, it has been reported previously in patients with overlapping phenotypes (Table 1) and was found in the affected tissue in this patient.

3 | Discussion

Extreme phenotypic variability is typical for mosaic disorders based on the developmental timing of the mutation, which impacts its distribution over the body [6]. Mosaic mutations in *KRAS* have been identified in various conditions with overlapping phenotypes, for xample, SFM syndrome and nevus sebaceus, OES, ECCL, low-flow vascular malformations, and arteriovenous malformations [1, 4, 5, 7, 8]. Specifically, a mosaic *KRAS* c.436G>A, p.(Ala146Thr) mutation, as found in our patient., has been previously reported only in OES and ECCL but not in SFM syndrome [5, 6]. Previously reported mosaic *KRAS* mutations in SFM syndrome include c.35G>A p.(Gly12Asp) and c.35G>T p.(Gly12Val) [3, 4, 9, 10].

Findings of SFM syndrome include craniofacial nevus sebaceus, and neurologic (mental retardation, seizures, hemimegaloencephaly), ocular (epibulbar tumors, colobomas), and skeletal (incomplete bony structures, vitamin D-resistant hypophosphatemic rickets) abnormalities. Cardiac malformations have been observed in up to 12% and genitourinary abnormalities in 10% of the patients [11, 12], which were not identified in our patient. In addition, vascular malformations and lymphedema have been reported in SFM syndrome [13]. SFM patients may present with symptoms seen in Noonan syndrome and other *RAS*opathies as our patient had lymphatic abnormalities [14, 15].

OES is a rare disorder characterized by unilateral or bilateral epibulbar dermoids and aplasia cutis congenita [5]. Additional ocular anomalies comprise upper eyelid skin tags, optic nerve, or retinal changes, and microphthalmia [16]. Ectodermal changes, classically linear blaschkoid hyperpigmented patches and epidermal nevi, can be present [5, 16]. Other findings include benign tumors such as nonossifying fibromas of the long bones and giant cell granulomas of the jaw [7]. OES may present with additional abnormalities for example, growth failure, lymphedema, cardiovascular defects, and neurodevelopmental symptoms [5, 16].

ECCL manifests with focal alopecia, epibulbar dermoid cysts, upper eyelid lesions, linear hyperpigmentation, and intracranial and intraspinal lipomas [17]. As in OES, jaw tumors and progressive bone cysts are reported in ECCL. Subcutaneous fatty masses in the frontotemporal or zygomatic region in ECCL are rarely reported in children diagnosed with OES [5]. A hairless fatty tissue nevus of the scalp (nevus psiloliparus) is considered the dermatological sign of ECCL [17, 18]. Altogether OES and ECCL are considered to belong to a disorder spectrum caused by mosaic mutations in *RAS*opathy genes [5, 6, 16].

Based on most clinical findings, including nevus sebaceus, hyperpigmented patches along blaschkoid lines, epibulbar dermoid, coloboma, benign cortical defect, lymphedema, abnormal lymphatic circulation and endocrinological findings, our patient was diagnosed with SFM syndrome but had overlapping features of OES and ECCL. Facial nevus sebaceus is a hallmark of SFM syndrome, while lymphedema has been reported less frequently [13]. Blaschkoid hyperpigmented patches are associated with OES and ECCL, but linear hyperpigmentation is also noted in SFM syndrome. Especially ocular findings have significant clinical overlapping in OES, ECCL and SFM syndrome [19]. Benign tumors such as nonossifying fibromas have been reported in all three syndromes. Intracranial and intraspinal lipomas are prominent features in ECCL but were also seen in our patient. Overall, our patient's clinical presentation is compatible with the diagnosis of SFM syndrome.

The highly variable and overlapping phenotypes of SFM, OES, and ECCL, and their emerging molecular etiologies, especially a common etiology as reported here, challenge the nosology

TABLE 1 | Clinical features of our patient and previously described patients with the same genetic mutation: Mosaic *KRAS* c.436G>A, p.(Ala146Thr).

	SFM[a]	OES[b]	OES[c]	ECCL[c]
Sex	Male	Female	Male	Male
Age at report (years)	15	4	6	5
Cutaneous findings				
Nevus sebaceus	+	NA	NA	NA
Scalp alopecia	+	+	+	+
Subcutaneous scalp lesions	−	NA	+	NA
Linear hyperpigmentation	+	+	+	+
Other	−	Polythelia	Linear hypopigmentation	Atopic dermatitis
Ophthalmological findings				
Epibulbar dermoid	+, unilateral	+, unilateral	+, bilateral	+, bilateral
Other	Upper eyelid coloboma	−	−	Everted, hypoplastic upper eyelids with skin tags
Musculoskeletal findings	Benign cortical defect of tibia	Left facial hemihyperplasia	NA	Several cystic lesions in the long bones of all extremities and clavicles
	−	−	−	Cystic paravertebral process Th10/Th11
Neurological findings	Intracranial and intraspinal lipomas	−	Enlarged cisterna magna and fluid space in the quadrigeminal cistern	Hemi-atrophy of left cerebral hemisphere and ventriculomegaly
	−	−	Intellectual disability, attention deficit hyperactivity disorder	No neurological symptoms
Cardiovascular	−	Atrial septal defect, persistent ductus arteriosus	NA	Aortic coarctation
Endocrinological	Delayed puberty Type 1 diabetes	−	−	Mild growth failure, relative macrocephaly
Vascular malformation	Lymphedema and abnormal lymphatic system (circulation, reflux)	NA	NA	NA
Other	−	−	−	Narrow left main bronchus causing partial atelectasis

Abbrevations: −, not present; +, present; ECCL, encephalocraniocutaneous lipomatosis; NA, not assessed; OES, oculoectodermal syndrome; SFM, Schimmelpenning-Feuerstein-Mims.
[a]This report (SFM).
[b]Patient #1 (OES) from Chacon-Camacho et al. [6].
[c]Patients 2 (ECCL) and 4 (OES) from Boppudi et al. [5].

and terminology in the field. Currently, facial nevus sebaceus is considered the hallmark of SFM, and nevus psiloliparus is the hallmark of ECCL, while the characteristic skin feature in OES is considered aplasia cutis congenita. To date, these dermatological findings are used to differentiate the syndromes, but to ensure more accurate diagnoses refining the classification system to integrate clinical findings with the underlying molecular etiology is needed. It would also improve treatment strategies, overall patient outcomes as well as research, and our understanding of the syndromes.

Here, we report a mosaic *KRAS* variant c.436G>A, p.(Ala146Thr) in a SFM patient. The same mutation was earlier described in association with OES and ECCL, and our patient shares many similar phenotypical features with those disorders. These clinical and genetic findings corroborate the SFM syndrome to be a mosaic *RAS*opathy and unravel and widen the phenotypic spectrum of mosaic *RAS*opathies.

Acknowledgments

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Consent

The patient provided written consent for the publication of this case report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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