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SCALP syndrome with a germline heterozygous *DOCK6* mutation and somatic mosaic *NRAS* Q61R mutation: case report and review of the literature

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Abstract

We present a case of SCALP syndrome, which was diagnosed in a male infant with the characteristic findings of sebaceous nevi, central nervous system malformations, aplasia cutis congenita (ACC), limbal dermoid, and giant congenital melanocytic nevi, or pigmented nevi. We identified a germline compound heterozygous *DOCK6* mutation and a somatic mosaic *NRAS* Q61R mutation in the giant congenital melanocytic nevus. This report will increase clinician awareness of SCALP syndrome and augment the literature in characterizing this rare syndrome, including its genetic background.

Keywords

SCALP; sebaceous nevi; aplasia cutis congenital; limbal dermoid; pigmented nevi; giant congenital melanocytic nevi

Introduction:

SCALP syndrome is a rare neurocutaneous disorder characterized by the co-occurrence of sebaceous nevi, central nervous system malformations, aplasia cutis congenita (ACC), limbal dermoid, and pigmented nevi/giant congenital melanocytic nevi (GCMN). There have been six cases of SCALP syndrome reported in the literature, with the first dating back to 1986 by Mimouni et al.[1] In the third reported case, Lam et al. proposed the

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acronym “SCALP” to represent this rare constellation of symptoms.[2] Prior to this, these cases were thought to be a variant of linear nevus sebaceous syndrome (LNSS), also known as Schimmelpenning syndrome. While these syndromes share clinical features including nevus sebaceous, ocular lesions, and cerebral defects, SCALP also encompasses ACC and GCMN. Herein, we present a case of SCALP syndrome, including genetic analysis.

Case Report:

A 12-year-old male presented to our pediatric dermatology clinic with multiple nevi and congenital anomalies. He was delivered via cesarean section to a non-consanguineous healthy couple. The family history was negative for any dermatologic, neurological, or musculoskeletal abnormalities.

He had a history of multiple cutaneous and ocular lesions that were histologically confirmed: (1) a large sharply demarcated light brown congenital nevus with overlying blond hair and foci of darker brown papules and macules involving the scalp, upper back, right upper chest sparing the areola (Figure 1A), right shoulder, posterior scalp and neck (Figure 1B) with multiple satellite lesions on the extremities; (2) several large verrucous yellowish plaques consistent with nevus sebaceous involving the left temporal area, forehead, cheek, and left eye that had been surgically resected; (4) one ovoid atrophic plaque on the posterior scalp consistent with aplasia cutis congenita that had been surgically excised, and (5) a yellowish papule on the left conjunctiva consistent with a limbal dermoid that had been surgically removed. The patient also had a history of a protuberant skull mass to the left parietal area consistent with an osteoma without features of fibrous dysplasia that was also previously excised.

During the time the patient was followed by our dermatology clinic, additional satellite nevi developed on the lower extremities, and there was darkening of the smaller papules located within the giant congenital nevus on the right shoulder and chest. Histological examination of these changes confirmed benign congenital nevi without evidence of malignancy.

The patient’s neurologic history was significant for multiple complications, including infantile spasms, dysplastic temporal lobe epilepsy, neurocutaneous melanosis, and temporal lobe malformations. Seizures began two weeks after birth, and an initial CT scan revealed meningeal thickening and an enhancing mass along the left occipital and temporal lobes that was concerning for neurocutaneous melanosis of the leptomeninges. A follow up MRA confirmed this, showing prominence of the choroid plexus and a punctate focus of increased T1 signal of the left brachial points thought to represent a melanin-containing nevus. There was also evidence of left temporal lobe malformations including polymicrogyria, pachygyria, band heterotropia, and hemimegaloencephaly.

A left eye limbal dermoid was surgically removed at age 4 years. Other ocular abnormalities included astigmatism and exotropia that resolved with eye patching. At age 10, the patient was noted to have a developmental delay of approximately three years behind his grade level, specifically in executive functioning and social skills. Psychiatric history included

impulse control disorder and anxiety. Musculoskeletal abnormalities included toe walking requiring surgical correction.

After informed consent and as part of genetic research, we performed mutation analysis of normal tissue on saliva specimen that revealed two germline compound heterozygous mutations in *DOCK6 (*R1208W and R1173W) and *HADHB* (R39H and R61H). There were also 50 other germline variants detected, all of which were likely not pathogenic (Table 2, supplementary material). Additionally, a skin biopsy of the GCMN revealed a pathogenic somatic heterozygous mutation in *NRAS* Q61R which was absent from normal tissue. There was also a somatic mutation in *IGFN1* (6079_6080 non-frame shift insertion) that was determined to be non-pathogenic by ClinVar. The patient was lost to follow up at 13 years of age.

Discussion:

Here we describe a patient with SCALP syndrome, associated with a germline compound heterozygous *DOCK6* mutation and a somatic mosaic *NRAS* Q61R mutation in the giant congenital melanocytic nevus. Although, Group 3 aplasia cutis congenita and LNSS associated with ACC, neurocutaneous melanosis, and a giant pigmented nevus was also considered. Group 3 Aplasia Cutis is characterized by scalp ACC, multiple epidermal and organoid nevi, ocular aberrations, psychomotor retardation, and seizures. ACC can develop sporadically or can be inherited in an autosomal recessive or dominant manner, with the latter being associated with the *BMS1* gene—a known player in skin morphogenesis.[3] LNSS was also on our differential diagnosis. However, while it encompasses nevus sebaceous, ocular lesions, and CNS defects, rarely is LNSS associated with ACC or GCMN. In fact, the six cases that describe LNSS associated with both GCMN and ACC are now reclassified as SCALP syndrome.[1,2,4–7] Additional rare diagnoses to consider in a neonate with ocular, cutaneous, and central nervous system abnormalities include oculocerebrocutaneous (Delleman Oorthuys) syndrome, encephalocraniocutaneous lipomatosis (Haberland syndrome), and oculoectodermal (Toriello-Lacassie-Droste) syndrome.

Among the germline variants identified in our presented case, *DOCK6* was suspected to be contributory to the patient's phenotypic presentation given its association with ACC in Adams-Oliver syndrome.[8] *DOCK6* is involved in the regulation of GTPases, a necessary component in signal transduction and tight control of embryonic development.[9] Autosomal recessive mutations in *DOCK6* are known to cause Adams-Oliver syndrome, a rare developmental disorder characterized by aplasia cutis congenita, vascular malformations, congenital heart defects, eye and limb deformities, and neurological deficits including structural brain defects and developmental delays.[8] As our patient had a compound heterozygous mutation in *DOCK6*, it is plausible that this germline mutation had some implication in the patient's ACC, eye anomalies, and/or CNS malformations. The other germline mutation detected in *HADHB* is unlikely to be contributory to our patient's phenotype as it is only associated with trifunctional protein deficiency, a metabolic disorder characterized by the inability to metabolize certain fats into energy, particularly during periods of fasting.

A somatic heterozygous pathogenic mutation in *NRAS* Q61R was also identified within the GCMN of our patient. Mutations at codon 61 in *NRAS* disrupt the GTP binding site and result in constitutive activation of the Ras-MAPK pathway leading to uncontrolled cell growth.[10] Individual somatic *NRAS* Q61R mutations have been described in GCMN (approximately half of cases), neurocutaneous melanosis (NCM), nevus sebaceous, and melanoma (CNS and cutaneous), whereas mosaic *NRAS* mutations, likely in neural ectodermal progenitor cells, have been described in LNSS[11] (although *HRAS* and *KRAS* are the most common),[12] congenital melanocytic nevus syndrome,[10,13] and one other case of SCALP syndrome reported by Chan et al (2018).[14] Chan et al (2018) described a male infant with cerebral malformations and extensive ocular defects with a mosaic *NRAS* mutation identified within the GCMN.[6] Similarly, in another case with a similar phenotype to our patient, the same mosaic *NRAS* Q61R mutation was identified.[15] However, while this patient had GCMN, sebaceous nevi, neurocutaneous melanosis, and ocular dermoids, he lacked ACC. The presence of ACC in our patient, while absent in this case, may be explained by the germline compound heterozygous *DOCK6* mutation which is associated with ACC. *NRAS* is potentially the genetic driver in the development of SCALP, given its implication in other epidermal RASopathy syndromes, and now two SCALP cases, including ours.[14]

Although the etiology of SCALP syndrome is unknown, Happle and Konig proposed twin spotting, or didymosis aplasticosebacea, to explain how an individual can have two or more different types of congenital nevi, like in SCALP syndrome.[16] In this theory, a heterozygous cell for two or more mutations undergoes somatic recombination in early embryogenesis to give rise to two daughter cells homozygous for each mutation. Another proposed mechanism is through a multilineage activating mutation, as seen in mosaic RASopathies. The mosaic *NRAS* mutations identified in two of the SCALP cases supports this hypothesis, although more research is needed to identify all genetic contributors in this rare phenotype.

Many similar features were shared between our patient and the six previously reported cases of SCALP syndrome (Table 1). Specifically, the sebaceous nevi commonly involved the left side of the scalp and face, often near the ACC lesions. The GCMN also spared the areola in all but two cases, likely because melanocytes and areolas have two different embryonic origins.[5] Additionally, all patients had some form of CNS malformations, often ipsilaterally in the left hemisphere (patient ID 1, 3, 4, 8; Table 1) or temporal lobe (patient ID 1, 3, 8; Table 1). Common cerebral abnormalities included neurocutaneous melanosis, hemimegaloencephaly, polymicrogyria, hydrocephalus, prominence of the choroid plexus, and CNS melanoma in one patient. Many also had seizures and/or developmental delays, while some had ocular and/or musculoskeletal defects.

Patients with SCALP syndrome should be followed closely due to the risk of malignancy and neurodevelopmental complications. Giant congenital melanocytic nevi have a 2–8%[17,18] risk of developing melanoma, thus it is imperative to regularly screen these patients for any new or changing cutaneous lesions. Sebaceous nevi are also at a 0.8–1.1% risk of developing an associated basal cell carcinoma.[18,19] While these lesions should also be monitored, the necessity to excise them is currently under debate. The extension of the lesion, the patient's age and their concern for cosmetic appearance should be all be considered when deciding

to excise sebaceous nevi. GCMN also carry a 3–12% risk of neurocutaneous melanosis (NCM) which can also develop into melanoma. Although NCM can be asymptomatic in some patients, it often presents with neurological complications such as increased intracranial pressure, seizures, psychiatric symptoms, and spinal involvement.[20–22] Baseline brain imaging should be obtained in SCALP patients given the risk of NCM and structural CNS defects, while any new neurological symptoms warrant further evaluation including a brain MRI.[23] Finally, SCALP patients should be evaluated by ophthalmology to monitor for any ocular abnormalities.

Herein, we present the first case of SCALP syndrome associated with a germline compound heterozygous *DOCK6* and mosaic *NRAS* Q61R mutation. This case will increase clinician awareness of SCALP syndrome and aid in characterizing this remarkably rare phenotype.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

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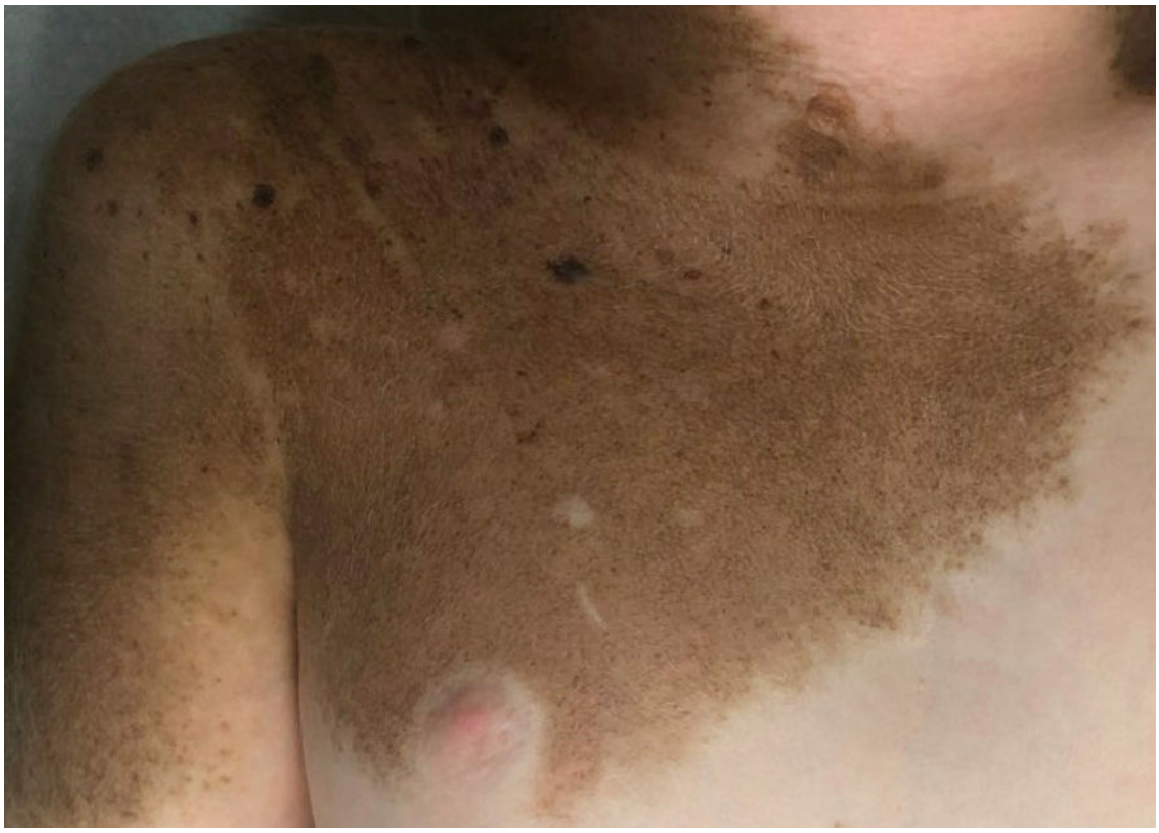

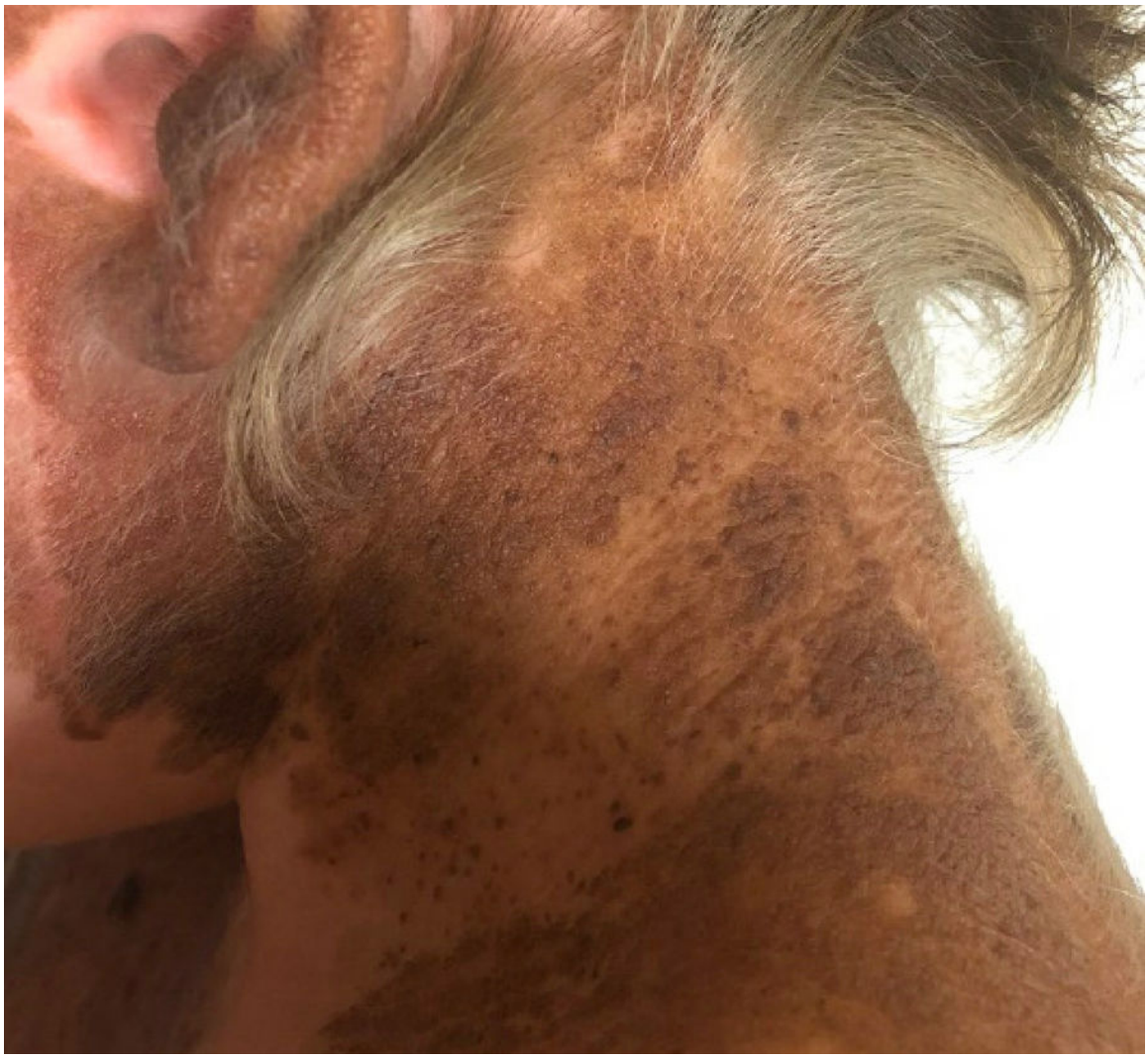

Figure 1A-B.
Congenital nevus involving the right chest (A) and left neck (B).

Table 1.

Published Cases of SCALP Syndrome.

ID	1st author, yr [reference]	Sex	Sebaceous nevus	GCMN†	CNS abnormalities	ACC‡	Ocular dermoids	Other findings	Mutations
1	Mimouni, 1986 [1]	M	L face, scalp	Scalp, R trunk *(sparing areola)* and shoulder, upper thighs	L hemimegaloencephaly, enlarged/ disorganized L temporal lobe, dysmorphic occipital horn of the L lateral ventricle, seizures, motor delay	2, scalp	Bilateral	Chondroma, hemangiomas, primitive benign neural tumors, nevus flammeus	
2	Török, 1988 [4]	F	Scalp, forehead	Scalp	Communicating hydrocephalus, seizures	4, scalp	Unilateral		
3	Lam, 2008 [2]	F	Scalp, L forehead	Scalp, chest, back with satellites on trunk (*sparing areolae*), face, limbs	NMS§, arachnoid cyst in L cranial fossa and spine, parenchymal enhancement of R medial temporal lobe, cerebellum, and pons, prominent choroid plexus in L hemisphere	Multiple, scalp	L eye	Patent ductus arteriosus	
4	Hsieh, 2012 [5]	F	L face, forehead, scalp	Face, scalp, trunk (*sparing areola*), L arm, satellites on R leg	1-cm dermoid cyst-like lesion in L cerebellopontine angle, high signal intensity in R parietal lobe	2, L temporal area	L eye	L wrist contracture	
5	Chan, 2018 [14]	F	Forehead, L scalp	L scalp and forehead, posterior neck, L back	Polymicrogyria of posterior parietal lobe and temporo-occipital cortex, abnormality of bilateral hemispheric white matter, parenchymal loss, seizures, developmental delay	1, L parietal bone	Bilateral	Esotropia, L optic nerve and optic chiasm hypoplasia, exposure keratopathy	Mosaic *NRAS* mutation in scalp congenital nevus
6	Esposito, 2019 [7]	M	Scalp, L hemiface	L anterior thorax and shoulder (*sparing areola)*, abdomen, scalp, face with satellites	CNS melanoma of frontoparietal region, intracranial hypertension, seizures	3, scalp	Bilateral		
7	Ramesh, 2017** [15]	M	2, nose	Face, scalp, trunk (including areola), upper arms, legs with satellites	NCM, developmental delay	Possible ACC on R scalp	R eye	Aphonia, CSHS†† syndrome	Mosaic *NRAS* Q61R mutation in GCMN and ocular dermoid
8	Present case	M	L temporal area, forehead, cheek, L eye	Scalp, neck, back, R upper chest and shoulder (*sparing the areola)*, satellites on extremities	NCM, L temporal lobe malformations, infantile spams, dysplastic temporal lobe epilepsy, developmental delay	1, scalp	L eye	Fibro-osseous lesion of parietal bone, astigmatism, exotropia	Mosaic *NRAS* Q61R mutation in GCMN; Germline *DOCK6* heterozygous mutation

† Giant congenital melanocytic nevus

‡ Aplasia cutis congenita

§ Neurocutaneous melanosis

** Although not classified as a SCALP case, this case had a similar presentation to SCALP. This patient had sebaceous nevus, CNS defects, a limbal dermoid, and GCMN. However, it is not clear whether this patient also had ACC.

†† Cutaneous-skeletal hypophosphatemia syndrome