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Phenotypic Spectrum of *GNA11* R183C Mosaicism

Donglin Zhang[1] | Luis Fernando Sánchez-Espino[2,3] | Marta Ivars[4] | Elena Pope[5] | Amy J. Nopper[6] | Lisa M. Arkin[1] | Megha M. Tollefson[7] | Cinzia E. Lavarino[8] | Maya Muldowney[1] | Nagore Gené Olaciregui[8] | Sonia Paco[8] | Beth A. Drolet[1] | Eulàlia Baselga[4]

[1]Department of Dermatology, School of Medicine and Public Health, University of Wisconsin, Madison, Wisconsin, USA | [2]Dermatology Department, Stollery Children's Hospital, Edmonton, Alberta, Canada | [3]Pediatrics Department, Faculty of Medicine & Dentistry, University of Alberta, Edmonton, Alberta, Canada | [4]Pediatric Dermatology Department, Barcelona Children's Hospital Sant Joan de Déu, Barcelona, Spain | [5]Division of Dermatology, Temerty Faculty of Medicine, The Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada | [6]Division of Dermatology, Children's Mercy, Kansas City, Missouri, USA | [7]Departments of Dermatology and Pediatrics, Mayo Clinic, Rochester, Minnesota, USA | [8]Molecular Oncology Department, Barcelona Children's Hospital Sant Joan de Déu, Barcelona, Spain

Correspondence: Beth A. Drolet (bdrolet@dermatology.wisc.edu)

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ABSTRACT

Background: Many vascular anomalies harbor postzygotic somatic variants in *GNAQ* and *GNA11*; however, the phenotype of specific G-protein variants has not been well described. We report the clinical characteristics of 17 patients with a *GNA11* R183C variant.

Methods: This case series is derived from a multinational cohort of vascular anomaly patients whose pathogenic mutations were identified using high-depth next generation sequencing. Data include vascular anomaly features, imaging reports, and extracutaneous manifestations of the *GNA11* R183C variant.

Results: We identified 17 subjects (median age 18 years [range 6–67]) with somatic *GNA11* R183C variant. All patients had vascular lesions of the skin that presented as pink-to-red in children and deeper red in adults. Most lesions were large, poorly demarcated, and reticulated patches that were often bilaterally distributed. Nevus anemicus was observed in 53% ($N=9$) and dermal melanocytosis in 13.3% ($N=2$) of individuals. 82% ($N=14$) of patients had limb growth discrepancies, and 1 patient had marked thoracic hypoplasia. 47% ($N=8$) of patients had facial involvement, and 41% ($N=7$) had forehead involvement. One patient experienced seizures due to right hemispheric leptomeningeal angiomatosis consistent with Sturge–Weber syndrome. Other findings included glaucoma (29%, $N=5$) and psychomotor delay (29%, $N=5$).

Conclusion: These findings contribute to our understanding of the clinical spectrum of *GNA11* R183C capillary malformations (CMs); patients characteristically present with extensive, bilateral, poorly demarcated, pink-to-red CMs associated with nevus anemicus. Glaucoma and growth discrepancies (overgrowth or undergrowth) are common. Leptomeningeal angiomatosis and developmental delay can occur, appearing potentially less prevalent and severe than *GNAQ*-associated disease.

Donglin Zhang and Luis Fernando Sánchez-Espino considered joint first authors.

Beth Drolet and Eulàlia Baselga considered joint senior authors.

1 | Introduction

Cutaneous capillary malformations (CMs), also known as port wine birthmarks (PWBs) or nevus flammeus, are the most common vascular malformation in the general population [1]. While these congenital, pink-to-red flat lesions may affect the skin in isolation, they can accompany tissue growth dysregulation or neurocutaneous syndromes such as the Sturge–Weber syndrome (SWS) [2, 3].

Whereas vascular malformations were historically viewed as errors of vasculogenesis, we now understand that genetic alterations in cellular growth and survival pathways variably drive these anomalies. In 2013, Shirley et al. identified somatic activating mutations in guanosine nucleotide-binding protein G(q) subunit alpha (*GNAQ*) in affected tissue from both Sturge–Weber syndrome and nonsyndromic vascular lesions [4]. Mutations in *GNA11*, a paralogue guanosine nucleotide-binding protein, have also been associated with CMs [5–7]. Even though *GNA11* shares 90% sequence homology and demonstrates functional overlap with its paralogue *GNAQ*, less is known about the clinical phenotype of CM patients affected by *GNA11* mutations compared to those with *GNAQ* mosaicism [8]. We present a case series of 17 patients to contribute to the literature regarding phenotypic features and the clinical course of children and adults with the *GNA11* R183C somatic mutation.

2 | Materials and Methods

Subjects were identified from a multinational cohort of patients with vascular anomalies. All collaborating sites obtained Institutional Review Board approval from their respective institutions. Subjects harboring the somatic *GNA11* R183C mutation, confirmed by high-depth targeted sequencing of the affected tissue, were included in this study. Medical history, demographic information, radiologic imaging, and clinical features were collected. Tissue sources for genotyping included formalin-fixed paraffin-embedded tissue and fresh frozen skin samples. Tissue genotyping was performed in Clinical Laboratory Improvement Amendments (CLIA)-approved laboratories or on a research basis using next-generation sequencing (NGS) as previously reported [9]. Digital PCR was performed in some cases with commercial and custom designed assays for detection of R183C variant in *GNA11* and *GNAQ* genes.

3 | Results

A total of 17 subjects (Table 1) had vascular lesions harboring the *GNA11* R183C mutation. All had low variant allele frequency (range 0.7%–8%) consistent with mosaicism. The median age was 18 years (range 6–67).

One subject's sample also harbored a *MAP2K2* p.H292R variant of unknown significance. Sequencing of a pyogenic granuloma that developed within a subject's vascular lesion revealed both *BRAF* V600E (VAF 6.4%) and *GNA11* R183C (VAF 5.67%) variants.

TABLE 1 | Summary of patient characteristics.

	***N*=17**
	***n* (%)**
Sex	
Female	9 (53)
Male	7 (41)
Anatomic locations affected by CM(s)	
Head/neck	9 (53)
Face	8 (47)
Bilateral face	6 (35)
Extremities	17 (100)
Trunk	15 (88)
Pattern of CM involvement	
Bilateral distribution	12 (71)
Extremities only[a]	1 (6)
Extremities and trunk[b]	7 (41)
Head/neck, trunk, and extremities	9 (53)
Concomitant skin findings	
Nevus anemicus	9 (53)
Dermal melanocytosis	2 (12)
Growth discrepancy of affected limb(s)	14 (82)
Overgrowth	10 (59)
Undergrowth	4 (24)
Associated findings	
Glaucoma	5 (29)
Leptomeningeal angiomatosis	1 (6)
Developmental/psychomotor delays	5 (29)

[a]Without trunk or head/neck involvement.
[b]Without head/neck involvement.

All subjects had vascular lesions, and most (94%, $N=16$) were poorly demarcated, reticulated pink-to-red patches (Figure 1). Many had nevus anemicus (53%, $N=9$) overlapping the vascular malformation (Figure 2). Most subjects had extensive cutaneous involvement; median affected body surface area was 35% (range 7.5%–85%), and bilateral distribution of vascular lesion(s) was common (71%, $N=12$). All patients within our cohort had CM(s) affecting at least one extremity, and 53% ($N=9$) on their head/neck and trunk in addition to their extremities. Facial involvement was seen in 47% ($N=8$) of patients; forehead involvement in 41% ($N=7$); and bilateral face involvement in 35% ($N=6$). Other skin findings included dermal melanocytosis in 12% ($N=2$) patients. Progressive darkening of the CM with age was observed in 59% ($N=10$) of cases. Superficial varicosities, thin vascular blebs, and upper extremity edema were found in adults ($N=3$) but not in pediatric patients. No café-au-lait macules or abnormalities of the teeth or hair were seen.

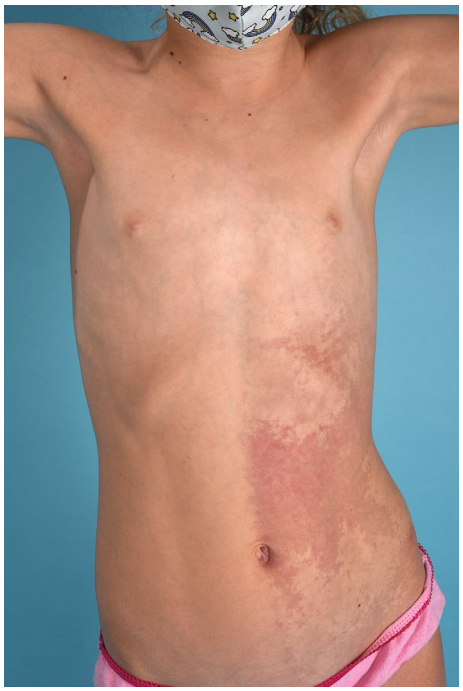

FIGURE 1 | Poorly demarcated, reticulated pink to red patches of the trunk.

FIGURE 2 | Uniform overgrowth with increased length and circumference of the left leg affected by CM harboring the *GNA11* R183C variant.

Growth discrepancy was seen in 82% ($N=14$) of subjects, typically presenting as uniform overgrowth of a vascular malformation-affected limb (67%, $N=10$; Figure 3). The degree of growth discrepancy, using length- and circumference-based provider assessment, ranged from 20% to 50% compared to the contralateral side. One patient underwent growth plate fusion for leg length discrepancy. Two patients (13%) demonstrated

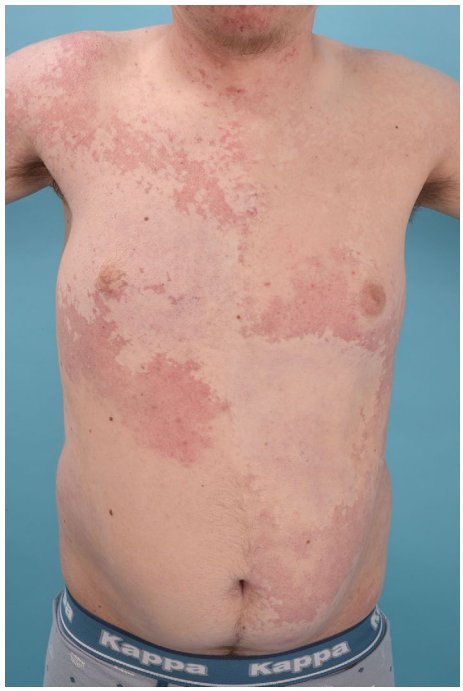

FIGURE 3 | Nevus anemicus at the border of a large capillary malformation of the trunk.

undergrowth of a vascular malformation-affected limb. One case each of clinodactyly, syndactyly, and sandal gap deformity was seen. In patients with facial vascular lesions, 38% ($N=3/8$) had macrocephaly and 25% ($N=2/8$) had macrocephaly associated with macrocheilia.

Glaucoma affected 29% ($N=5$) patients, all of whom had lesion involvement of their bilateral face, including forehead (80%, $N=4/5$) or eyelid (60%, $N=3/5$). Psychomotor or neurodevelopmental delays were seen in 29% ($N=5$) of the cohort, presenting in early childhood as motor milestones delay ($N=2$), language/speech and learning deficits ($N=5$), dyslexia ($N=1$), and/or ADHD ($N=2$). Patients with facial CM(s) comprised 60% ($N=3/5$) of patients with developmental delays.

Brain magnetic resonance imaging (MRI) was completed for 53% ($N=9$) of all patients. Facial involvement of vascular lesions was present in 77% ($N=7/9$) of these cases, 86% ($N=6/7$) of whom had abnormal findings on MRI, including engorgement of the choroid plexus ($N=3$), presumed cavernoma/telangiectasia in the right hemipons ($N=1$), diffuse white matter loss ($N=1$), increased white matter signal intensity in FLAIR/T2 sequences ($N=2$), and leptomeningeal angiomatosis ($N=1$). The patient with the cavernoma experienced headaches, and the patient with leptomeningeal angiomatosis experienced intermittent episodes of left-sided weakness beginning at age 3 years, consistent with SWS and was placed on low-dose aspirin and antiepileptics.

Five (29%) patients developed hypertension. Two patients with documented hyperaldosteronism developed hypertension prior to age 18 years, one patient without confirmed hyperaldosteronism developed hypertension prior to age 18 years, and two patients experienced gestational hypertension. One subject had bilateral renal artery stenosis, and one subject had tortuous intraparenchymal vessels in the left kidney.

4 | Discussion

GNAQ and *GNA11* are paralogous genes that encode proteins that comprise the Gαq and Gα11 nucleotide-binding subunits of heterotrimeric G proteins. Activating mutations dysregulate several important intracellular signaling pathways [4, 9]. Recent studies of inherited hypocalcemia and hypercalcemia caused by genomic mutations in *GNA11* but not *GNAQ* hints that *GNAQ/GNA11* nonoverlapping functions are present [10–14]. It is well known that activating mutations in both *GNAQ* and *GNA11* are associated with capillary malformations; however, few studies have detailed phenotypic differences in the presentation, severity, and prognosis between patients with *GNA11* and *GNAQ* driven vascular lesions.

We further elucidate the phenotype associated with the mosaic *GNA11* R183C mutation by detailing the clinical findings of in a cohort of 17 patients from two international vascular anomalies cohorts. The cutaneous vascular lesions were all diagnosed as CMs; however, distinctive clinical features were identified. The lesions were pink-to red in color with patchy and reticulated borders. The lesions were often large and bilateral in distribution. These findings are consistent with previous smaller case series [15]. Additionally, the finding of concomitant nevus anemicus in 53% of our cohort suggests a strong association between this entity and CMs harboring *GNA11* R183C [13, 16]. A prior study noted nevus anemicus in only four of 20 patients with activating mutations at the *GNAQ* R183 locus and in 12 of 12 patients with *GNA11* R183C mutation [17]. Similar to previous reports, two patients within our cohort also had dermal melanocytosis, consistent with a diagnosis of phakomatosis pigmentovascularis (cesioflammea, achromico-melano-marmorata, and cesiomarmorata) [18].

Limb length discrepancy was common among our cohort: 10 patients had hypertrophy, and four patients had ipsilateral limb hypotrophy. Ipsilateral segmental hypotrophy may be more specific for *GNA11* [17]. In their study, Jordan et al. investigated the range of phenotypes associated with CM linked to mutations in *GNAQ* or *GNA11* [17]. They observed that all four patients displaying segmental hypotrophy exhibited mutations at the *GNA11* R183 locus.

In this series, five patients developed hypertension, three prior to adulthood and two patients had gestational hypertension. We previously reported early-onset hypertension in 17% of patients with CMs harboring somatic GNAQ/GNA11 mutations [16, 17, 19]. The cause of this association is not understood and may be multifactorial as both renal anomalies and abnormal calcium metabolism have been reported [12, 13, 17, 18]. Zecchin et al. suggest that GNAQ/GNA11 mosaicism lead to aberrant intracellular calcium signaling in endothelial cells, a process that may underly premature vascular calcification [10].

The anatomic distribution of CM(s) may relate to the cell lines involved in the pathogenesis of the vascular lesions and has important implications for prognosis and screening for noncutaneous disease [5, 20, 21]. Previous studies have described increased glaucoma risk in patients with eyelid CMs and even greater risk in patients with bilateral facial CMs [22]. Our cohort supports these findings as all five patients with glaucoma had bilateral facial lesions.

Prior studies have demonstrated that forehead CMs are associated with greater risk of SWS [23, 24]. Within our cohort, one of seven patients with a forehead CM developed seizures and had associated leptomeningeal angiomatosis on brain MRI, consistent with a diagnosis of SWS. Previous publications suggest neurologic symptoms associated with facial CMs harboring *GNA11* R183C are less severe compared with *GNAQ* R183. *GNAQ* variants appear to predominate in classic SWS, whereas *GNAQ* and *GNA11* variants are more evenly represented in phakomatosis pigmentovascularis-dermal melanocytosis [4, 16–18]. Collectively, we hypothesize that individuals with *GNA11* R183C mosaicism impacting the CNS may experience less pronounced neurological sequelae compared to those with *GNAQ* R183 CNS mosaicism. However, larger prospective studies incorporating comprehensive CNS imaging and neurocognitive assessments are needed to confirm this hypothesis.

4.1 | Clinical Recommendations

Patients with CMs with clinical features suggestive of *GNA11* R183 mosaicism should follow the same recommendations as those with suspected *GNAQ* mutations. Those with forehead and/or bilateral face involvement, macrocephaly, and/or concern for developmental delay should undergo ophthalmologic and neurologic evaluation, including early brain MRI including FLAIR and SWI-Bold sequences for detecting CNS abnormalities [22]. Pediatric patients should be closely monitored for neurodevelopmental delay or behavioral issues, as these should prompt formal evaluation by a neurologist and/or developmental pediatrician, with implementation of appropriate psychosocial support.

We recommend that all patients diagnosed with CMs suggestive of *GNAQ*/*GNA11* mosaicism, regardless of age, have their blood pressure measured at the time of diagnosis and at each follow-up visit to monitor for development of hypertension. Patients found to have hypertension should have further workup with renal Doppler ultrasound. Patients should be screened for calcium metabolism dysregulation and hyperaldosteronism at the time of diagnosis with serum aldosterone to renin ratio (ARR; values above 30 ng/dL are suggestive of hyperaldosteronism) and, if normal, every 1–2 years thereafter (or earlier in the case of signs/symptoms). Any abnormal results should be followed by an endocrinologist.

Patients should be evaluated for limb growth discrepancies and other musculoskeletal anomalies. Suspicion for limb hypo- or hypertrophy should be monitored yearly by an orthopedic surgeon as surgical and nonsurgical interventions might be warranted.

5 | Conclusion

This case series adds to the current understanding of clinical phenotypes and radiological manifestations in patients with *GNA11* R183C mosaicism. Our findings support previous studies suggesting subtle phenotypic differences specific to patients with *GNA11* R183C postzygotic somatic mosaicism, including

extensive, bilateral light pink reticulated CMs often associated with nevus anemicus or undergrowth of limbs affected by vascular lesions. We hypothesize that leptomeningeal involvement due to *GNA11* variants may be uncommon, and seizures may be less severe and have a later age of onset compared to *GNAQ* variants.

These findings highlight the importance of characterizing phenotypic features of somatic mosaic *GNA11* R183C to provide additional insight into the functional and prognostic implications for patients with vascular anomalies harboring this genetic variant. Prospective natural history studies with both molecular and clinical features are needed to better inform screening, prognostication, and therapy for patients.

5.1 | Limitations of the Study

Our study is limited by the retrospective nature, small number of participants, and lack of longitudinal outcomes. Larger, multisite prospective natural history are needed to have more robust information to establish surveillance and treatment guidelines.

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Ethics Statement

All collaborating sites obtained Institutional Review Board approval from their respective institutions.

Consent

Complete written informed consent was obtained from the patient for the publication of this study and accompanying images.

Conflicts of Interest

Beth A Drolet is the Co-founder and Board of Director at Arkayli Biopharma. Lisa M Arkin has no conflicts relevant to this study but is PI for research studies funded by Eli Lilly and Amgen, and receives consulting fees from Merck, Sanofi/Regeneron, and Nobel Pharma. DZ, LFSE, MI, EP, AJN, MMT, CEL, MM, NGO, SP, and EB have no conflicts to disclose.

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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