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Early-onset hypertension associated with extensive cutaneous capillary malformations harboring postzygotic variants in *GNAQ* and *GNA11*

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Abstract

Background and Objectives: Cutaneous capillary malformations (CMs) describe a group of vascular birthmarks with heterogeneous presentations. CMs may present as an isolated finding or with other associations, including glaucoma and leptomeningeal angiomatosis (i.e., Sturge–Weber syndrome) or pigmentary birthmarks (i.e., phakomatosis pigmentovascularis). The use of targeted genetic sequencing has revealed that postzygotic somatic variations in *GNAQ* and *GNA11* at codon 183 are associated with CMs. We report five patients with early-onset hypertension and discuss possible pathogenesis of hypertension.

Methods: Twenty-nine patients with CMs, confirmed *GNAQ/11* postzygotic variants, and documented past medical history were identified from a multi-institutional vascular anomalies study. Early-onset hypertension was defined as hypertension before the age of 55 years. Clinical data were reviewed for evidence of hypertension, such as documentation of diagnosis or elevated blood pressure measurements.

Results: Five of the 29 patients identified as having *GNAQ/11* postzygotic variants had documented early-onset hypertension. Three individuals harbored a *GNAQ* p.R183Q variant, and two individuals harbored a *GNA11* p.R183C variant. All individuals had extensive cutaneous CMs involving the trunk and covering 9%–56% of their body surface area. The median age of hypertension diagnosis was 15 years (range 11–24 years), with three individuals having renal abnormalities on imaging.

Conclusions: Early-onset hypertension is associated with extensive CMs harboring somatic variations in *GNAQ/11*. Here, we expand on the *GNAQ/11* phenotype and hypothesize potential mechanisms driving hypertension. We recommend serial blood pressure measurements in patients with extensive CMs on the trunk and extremities to screen for early-onset hypertension.

Olivia M. T. Davies and Ashley T. Ng contributed as co-first authors.

KEYWORDS
capillary malformation, GNA11, GNAQ, hypertension

1 | INTRODUCTION

Cutaneous capillary malformations (CMs) harboring pathogenic postzygotic variants in genes encoding guanine nucleotide-binding protein (G-protein) subunit alpha represent a broad spectrum of disease that can include soft tissue overgrowth, dermal melanocytosis (i.e., phakomatosis pigmentovascularis), and neurologic or ocular diseases (i.e. Sturge–Weber syndrome).[1–6] G-proteins and G protein-coupled receptors mediate cellular signaling critical to several biologic processes, including gene expression and cell division. The genes *GNAQ* and *GNA11* encode for highly conserved members of the G-protein subunit alpha-q family, Gq and G11, respectively. Postzygotic variations in these genes have been implicated in dysregulated endothelial cell signaling.[7,8]

We present a series of five patients with cutaneous CMs, postzygotic *GNAQ/11* variants, and early-onset hypertension. We review possible mechanisms to explain the association between the development of CMs and early-onset hypertension.

2 | MATERIALS AND METHODS

2.1 | Study population

Patients were identified from an IRB-approved, multi-institutional vascular anomalies cohort comprised of 383 individuals who provided informed consent at the time of this investigation. Medical history and demographic information were collected and stored in a secure REDCap database. Individuals identified as having a cutaneous CM harboring a pathogenic variant in *GNAQ/11* confirmed by high-depth targeted sequencing and documented history of hypertension were considered for inclusion (Figure 1). For this case series, early-onset hypertension was defined as hypertension before the age of 55 years. Evidence of hypertension was supported by (a) two or more measurements of systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥80 mmHg or (b) two or more measurements of systolic or diastolic blood pressures ≥95th percentile for children under 13 years of age. Renal ultrasound findings were reported for all included patients when available.

2.2 | Sequence analysis

DNA was extracted from fresh frozen or formalin-fixed tissue and assayed via high-depth next-generation sequencing following target enrichment for cancer-associated genes.[9] One sample was analyzed at a CLIA-approved laboratory while the other four samples were sequenced on a research platform using the same target capture panel.

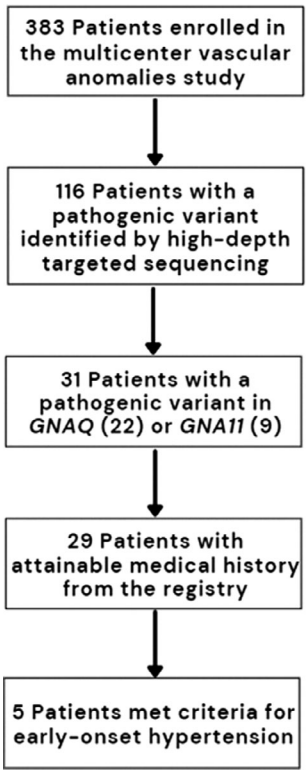

FIGURE 1 Flowchart of the study population

3 | RESULTS

Of the 29 patients identified as having a *GNAQ/11* postzygotic variant with available past medical history, five patients, of whom three were females, had documented concomitant early-onset hypertension and are included in this report (Table 1).

All five patients had large, widespread CMs involving the trunk and at least one extremity, with variable involvement of the face, neck, and additional extremities. The estimated area of involvement for these patients ranged from 9% to 56% of their body surface area. Cutaneous characteristics of the CMs varied within and among patients and ranged anywhere from classic deep red, blotchy, or block-like patches to more reticulate phenotypes (Figure 2). Dermal melanocytosis was observed in two patients.

Targeted sequencing identified two pathogenic variants: *GNAQ* p.R183Q ($n = 3$) and *GNA11* p.R183C ($n = 2$). Three patients (patients 2, 4, and 5) had Sturge–Weber syndrome associated with seizures, glaucoma, or structural brain abnormalities on MRI (e.g., pial angiomatosis, pituitary abnormality). All patients demonstrated venous ectasia and overgrowth of the affected tissue. Size discrepancies between affected and unaffected tissue of up to 30% difference were seen in our cohort, which may be a result of a greater proportion of cells expressing pathogenic variants (mean variant allele frequency of 4.4%).

TABLE 1 Clinical summary of patients with cutaneous capillary malformations harboring *GNAQ/11* postzygotic variants

Patient	Gender	Affected gene and variant	VAF	Body areas affected by CMs	Affected BSA (%)	Other cutaneous findings	Glaucoma	Brain MRI	Age at diagnosis of hypertension	Hypertension severity[a] (mmHg)	Renal imaging
1	F	*GNAQ* p.R183Q	5.8%	Neck, right chest, back, arms, right leg	40%	Dermal melanocytosis	No	N/A	13	140s/100s (stage 2)	Renal venous congestion on US Nephromegaly (right > left); T2 hyperintense venous malformation in right hilum on MRA
2	F	*GNA11* p.R183C	6.5%	Right face, right neck, chest, back, arms, legs	56%	None	Yes	Mild right-sided leptomeningeal angiomatosis	15	130–140s/90–110s (stage 2)	Nephromegaly (right > left) and bilateral cystic kidneys on US
3	F	*GNAQ* p.R183Q	4.2%	Right back, buttocks, right leg	9%	Nevus of Ota	No	N/A	24	130s/70s (stage 1)	Normal US
4	M	*GNAQ* p.R183Q	4.0%	Face, arms, chest, back	45%	None	No	Right-sided pial angiomatosis	11	110s/80s (stage 1)	Renal calcium deposits and simple cysts on US
5	M	*GNA11* p.R183C	1.7%	Face, chest, back, abdomen, arms, legs	38%	None	Yes	Pituitary abnormality; subtle volume loss and signal change in the right pons	17	130s/90s (stage 2)	Normal US

Abbreviations: BSA, body surface area; CM, capillary malformation; MRA, magnetic resonance angiography; US, ultrasound; VAF, variant allele frequency.
[a]At the time of diagnosis of hypertension.

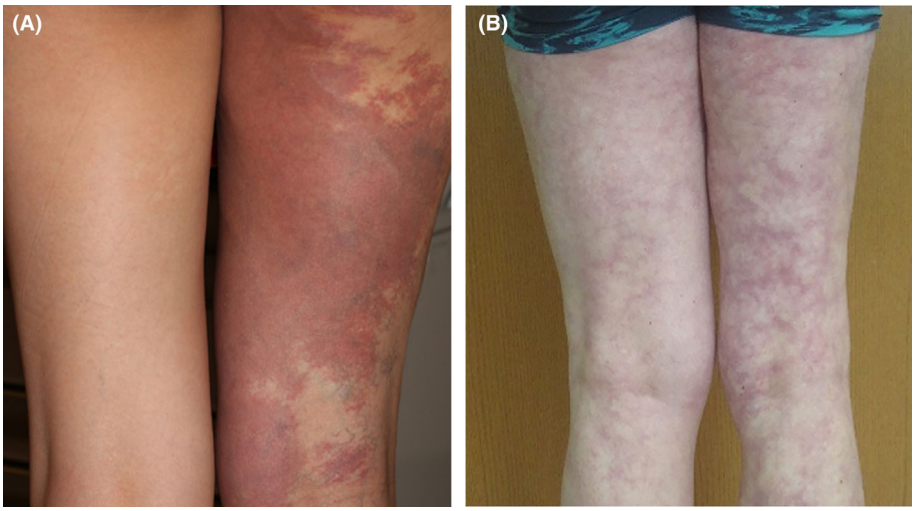

FIGURE 2 GNAQ/11 variants were associated with diverse clinical phenotypes, including deeply saturated, blotchy segmental red patches (A), and pink-red reticulate stains (B), all importantly affecting the trunk and extremities.

The median age at diagnosis of hypertension was 15 years (range 11–24 years). At the time of diagnosis, two patients demonstrated stage 1 hypertension while three had stage 2 hypertension according to the 2017 American College of Cardiology/American Heart Association Clinical Practice Guidelines for the Management of High Blood Pressure in Adults and the 2017 American Academy of Pediatrics Clinical Practice Guidelines for Management of Hypertension in Children and Adolescents.[10,11]

Laboratory studies and imaging findings varied between individuals. All five patients included in this series underwent renal ultrasound with more than half (three-fifths) demonstrating renal abnormalities. These included renal venous congestion, calcium deposits, and cystic changes.

Two of the three patients with stage 2 hypertension underwent additional workups. Patient 1 had an MRA of the abdomen that revealed a renal size discrepancy and a T2 hyperintense slowly enhancing venous malformation in the right renal hilum. She had additional workup that showed elevated plasma renin levels up to 22 ng/ml/h and mild left ventricular dilatation on echocardiogram. Patient 5 had additional workup for refractory hypertension which revealed an elevated urinary aldosterone excretion of 20 mcg/24 h consistent with hyperaldosteronism. CT imaging of his adrenals revealed normal-appearing adrenal glands. No other patients in this cohort had workup for hyperaldosteronism.

Three patients required medical management of their hypertension (patients 1, 2, and 5), who all had stage 2 hypertension at the time of diagnosis. Patient 1 required a two-medication antihypertensive treatment regimen with amlodipine and benazepril. Patient 2 was treated with amlodipine to control her diastolic blood pressure. Patient 5 was initially started on lisinopril but changed to eplerenone in the setting of his new diagnosis of hyperaldosteronism.

4 | DISCUSSION

Hypertension is a complex, multifactorial disease with well-established causes including atherosclerosis, family history of hypertension, increased age, and obesity. The estimated prevalence of stage 1 and 2 hypertension in children using the 2017 American Academy of Pediatrics Guidelines are 5.3% and 0.4%, respectively.[12] Current pediatric guidelines recommend blood pressure screening as part of the annual physical examination starting at age 3 years, while "selective screening" based on risk assessment prior to age 3 may be considered on an individual basis.[13] Hypertension screening is not conventionally included in the workup of patients with CMs, nor is it widely recognized as a part of the known clinical syndromes (e.g., Sturge–Weber) associated with postzygotic variants in *GNAQ/11*. Two recent publications note hypertension in 9%–16% of patients with postzygotic variants in *GNAQ/11*, suggesting that this is not merely an anomalous finding but a clinically relevant association.[5,6] Similarly, our study identified coexisting early-onset hypertension in 17% (5/29) of patients with postzygotic variants in *GNAQ/11*. Importantly, this may be an underrepresentation of the true prevalence as not all our patients were prospectively screened for hypertension, some are still young children, and some have been lost to follow-up.

Understanding of the downstream molecular effects of *GNAQ/11* postzygotic variants on systemic blood pressure regulation is incomplete, though a few theories illuminate the possible connection between this association. One theory focuses on the disruption of embryonic vessel morphogenesis. Couto et al.[7] found that endothelial cells from CMs are enriched for the *GNAQ* p.R183Q variant, and as such, the variant's effect on these cells is likely responsible for the underlying pathogenesis of CMs. Others have demonstrated that *GNAQ/11* p.R183 variants disrupt embryonic vessel morphogenesis resulting in vessel dilation and thickening, bulging, and discontinuities in the endothelium observed in CMs.[14,15] These endothelial aberrancies produce the clinical phenotype and, when widespread, may increase total peripheral resistance resulting in elevated blood pressure.

Another theory focuses on the role of *GNAQ/11* in calcium homeostasis. Loss-of-function germline variations in *GNA11* lead to alterations in cell sensitivity to extracellular calcium concentrations and may contribute to the development of hypocalciuric hypercalcemia.[16] The effect of gain-of-function variations in *GNAQ/11* has not yet been studied and serum calcium imbalances have not been documented in patients with cutaneous CMs associated with postzygotic

variations in *GNAQ/11*. However, early-onset intracranial calcification is a well-documented feature of Sturge–Weber syndrome, and one of our cases (patient 3) had renal calcium deposits.

Recently, molecular investigations have found that human endothelial cells of CMs harboring the *GNAQ* p.R183Q variant lead to constitutive activation of phospholipase C (PLC), promoting the expression of proangiogenic downstream targets of the nuclear factor kappa B (NF-κB) signaling pathway, most importantly angiopoietin-2 (ANGPT2).[8] ANGPT2 was shown to be a critical driver of vessel enlargement and distortion that may impact blood flow and permeability in blood vessels comprised of cells expressing *GNAQ* p.R183Q.

GNAQ/11 also mediates the adrenal aldosterone response to angiotensin II by facilitating release of intracellular calcium.[17] Genotyping of adrenal adenomas has identified somatic variants in *GNAQ/11*, specifically at p.Q209, and co-occurring *CTNNB1* mutations, supporting a 'double mutant' pathogenesis of these aldosterone-producing adenomas.[18] Perhaps postzygotic mosaicism of *GNAQ/11* in ipsilateral adrenal glands of patients with CMs predisposes them to the development of aldosterone-producing adenomas. At the time of publication, only one of our patients underwent evaluation for primary aldosteronism, which was positive. An extensive review of the literature did not identify additional cases, regardless, all patients with early-onset hypertension should be screened for hyperaldosteronism and other secondary drivers of hypertension.

Though these seem to be the most compelling, other theories exist to explain this association. For example, downstream signaling resulting from interactions between G-protein coupled receptors (GPCRs) and GPCR kinases may regulate vascular smooth muscle vasoconstriction and vasodilation.[19,20] In 2008, Wirth et al.[21] showed that G-proteins, namely Gq and G11, help mediate myosin light chain phosphorylation and, when mutated, can lead to increased vascular tone.

4.1 | Limitations

Given the lack of previous recognition of hypertension as a possible association, not all patients with pathogenic variations in *GNAQ/11* were systematically screened for hypertension, and this likely has resulted in an underestimation of its true frequency. Enrolled patients are not followed longitudinally, so those individuals who have developed hypertension since the time of their enrollment may have been missed. In addition, medication-related adverse effects on blood pressure were not assessed.

5 | CONCLUSIONS

Based on this case series and previous reports, early-onset hypertension appears to be a reproducible and valid association in individuals with large CMs involving the trunk with or without the involvement of other body parts. Molecular studies have helped to explain the possible causative pathogenesis of this phenomenon. Given the relative ease of screening for hypertension, we emphasize the importance of regular blood pressure measurements in individuals with CMs driven by postzygotic variants in *GNAQ/11* and early consideration for further workup and referral to nephrology when early-onset hypertension is identified.

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CONFLICTS OF INTEREST

Beth A. Drolet is a consultant to Venthera, the site principal investigator for a phase 1 clinical trial for the treatment of venous malformations, and the co-founder of ARKAYLI. Ilona J. Frieden is a consultant to Novartis and serves on the Data and Safety Monitoring Board for Pfizer. The remaining authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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