Hypertrichotic patches as a mosaic manifestation of Proteus syndrome

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Background: Proteus syndrome is an overgrowth disorder caused by a mosaic activating *AKT1* variant. Hair abnormalities in Proteus syndrome have rarely been reported, and frequencies of such findings have not been elucidated.

Objective: To define the types and frequencies of hair findings in individuals with Proteus syndrome.

Methods: A cross-sectional study was conducted of individuals with clinical features of Proteus syndrome and a confirmed pathogenic variant in *AKT1* evaluated between November 1996 and June 2019 at the National Institutes of Health Clinical Center. Medical records were reviewed for patterning, density, and color of hair on the body and scalp.

Results: Of 45 individuals evaluated, 29 (64%) had asymmetric hypertrichosis on the body. This included unilateral blaschkoid hypertrichotic patches overlying normal skin or epidermal nevi in 16 (36%), unilateral nonblaschkoid hypertrichotic patches in 11 (24%), and unilateral limb hypertrichosis in 10 (22%). Diffuse, scattered, or patchy changes in scalp hair density or color were present in 11 individuals (24%).

Limitations: The retrospective, observational design, and limited longitudinal follow-up.

Conclusions: Asymmetric variations in hair distribution, thickness, length, and color contribute to the overall mosaic appearance of the skin in Proteus syndrome, an observation that provides novel insights into the role of phosphoinositide 3-kinase (PI3K)-protein kinase B (AKT) signaling in skin appendage development. (J Am Acad Dermatol 2021;84:415-24.)

Key words: AKT; *AKT1*; Blaschko lines; hair; hair follicles; hypertrichosis; mosaicism; Proteus syndrome.

Proteus syndrome is a genetic condition characterized by progressive and asymmetric overgrowth of the skin, soft tissues, bones, and various organs. The disorder is extremely rare, affecting fewer than 1 per 1 million individuals, and it is diagnosed clinically by the presence of specific

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diagnostic criteria. An array of dermatologic features, including cerebriform connective tissue nevus, epidermal nevus, subcutaneous adipose dysregulation, and vascular malformations, comprise the clinical diagnostic criteria for Proteus syndrome.[1] Individuals with the disorder may also manifest patchy dermal hypoplasia,[2] nonpalpable pigmentary alterations, nail changes, and oral mucosal and dental findings.[3]

Proteus syndrome is caused by a mosaic activating variant in *AKT1*,[4] a gene that plays vital roles in cell cycle progression, cell survival, and apoptosis. In mosaic disorders, a postzygotic variant occurs within a single cell whose daughter cells differentiate into 1 or more tissues during prenatal development.[5] Mosaicism may alter the appearance of regions of skin containing cells affected by the pathogenic variant, and skin involvement is typically asymmetric with respect to the midline, with affected regions generally following specific discernible patterns. In Proteus syndrome, for example, certain cutaneous findings, most notably epidermal nevi, commonly follow the lines of Blaschko.[3] Other mosaic patterns include phylloid, checkerboard, and patchy.[6] Recognition of such cutaneous patterning is particularly useful for clinically detecting mosaicism.

In mosaic disorders, individuals with the same pathogenic variant may manifest variable distribution, tissue involvement, and severity of clinical findings. The resultant phenotypes are attributed to the particular cell lineages containing the pathogenic variant, which is in turn determined by the timing and location of the mutational event during embryogenesis.[7] Tissues affected in Proteus syndrome can include those that differentiate from all 3 embryonic germ layers. For example, ectoderm-derived keratinocytes and mesoderm-derived dermal fibroblasts containing the *AKT1* activating variant are key drivers in the formation of epidermal nevus or cerebriform connective tissue nevus, respectively.[8]

Hair follicles are regulated by complex interactions of mesenchymal and epithelial cells, raising the possibility for diverse types of hair changes in Proteus syndrome. However, despite the numerous descriptions and characterizations of skin abnormalities in Proteus syndrome, little is known about hair in this disease. We hence sought to determine the range and prevalence of hair abnormalities in a cohort of individuals with a molecular diagnosis of Proteus syndrome.

CAPSULE SUMMARY

- The diagnosis of Proteus syndrome frequently involves identification of skin lesions comprising specific criteria, and sampling affected skin is useful for genetic analysis.
- Most individuals with Proteus syndrome have hypertrichosis in an asymmetric distribution, a finding that should prompt consideration of this disorder and mosaic activation of phosphoinositide 3-kinase (PI3K)-protein kinase B (AKT) signaling.

METHODS

Individuals were evaluated for Proteus syndrome at the National Institutes of Health Clinical Center in Bethesda, Maryland, from November 5, 1996, to June 13, 2019. Informed consent was obtained according to protocol 94-HG-0132, which was approved by the National Genome Research Institute Institutional Review Board at the National Institutes of Health.

A retrospective review of written medical records and clinical photographs was conducted of individuals with clinical features of Proteus syndrome and genetic analysis of affected tissue confirming presence of the mosaic c.49G>A, p.Glu17Lys variant of *AKT1*. This activating variant of *AKT1* is considered pathogenic for Proteus syndrome.[4] The presence or absence of clinical findings relating to patterning, density, speed of growth, and color of hair on the scalp and body was recorded. We additionally noted the distribution and patterning of each finding as well as any other unusual or distinctive dermatologic features.

RESULTS

There were 51 individuals with clinical features of Proteus syndrome who had the mosaic c.49G>A, p.Glu17Lys variant of *AKT1*, and 45 had adequate written records or photographs to assess the full body for hair aberrations. There were 28 males and 17 females, with a median age of 7 years (range, 2-40 years).

Hair changes observed in our cohort are summarized in Table I. The most frequent finding was asymmetric hypertrichosis, seen in 29 of the 45 individuals (64%). This was defined by grossly increased hair thickness and/or length on one region of skin relative to the same area on the contralateral part of the body.

The most frequently observed pattern of hypertrichosis followed the lines of Blaschko (Fig 1), which was observed in approximately one-third of the 45 individuals assessed. In most individuals,

Abbreviations used:

AKT: protein kinase B
PI3K: phosphoinositide 3-kinase

this appeared in a linear distribution extending from the upper trunk to the proximal arm, although single instances each were observed on the lower back, flank, jaw line, or anterior chest. The underlying skin associated with these patches displayed a spectrum of appearances, which included normal appearing; flat, slightly hyperpigmented (Fig 1); minimally elevated, velvety, moderately pigmented (Fig 2); and thick, deeply pigmented, mamillated, verrucous plaque.

Nonblaschkoid patches of unilateral hypertrichosis were present in 11 of the 45 individuals (24%). These were heterogeneous in size, morphology, and location, and a few individuals had several of these hypertrichotic patches. They were observed on the trunk in 5, leg in 4, arm or hand in 3, shoulder in 2, and neck in 1. Notably, 2 were on the dorsal aspect of the hand or arm overlying a connective tissue nevus, 2 were associated with an epidermal nevus on the anterior neck and anterior chest, respectively, and 1 was superimposed upon a capillary-venous malformation on the lateral leg.

In 10 of 45 individuals, hypertrichosis was present on most of one limb relative to the other (Fig 3). This feature was present on a leg in 9 of the 10 individuals, and it almost always (9 of 10) occurred on an overgrown limb. Two individuals reported asymmetric speed of hair growth; 1 reported this finding on the face and the other on the leg. Two individuals had increased hair density in one axilla relative to the other.

Changes in scalp hair density were present in 5 of the 45 individuals (11%). Two individuals had round alopecic patches; 1 had partial alopecia overlying an exostosis, and 1 had focal, complete alopecia due to aplasia cutis congenita. Two individuals had diffusely decreased hair density, and 1 child had asymmetric density of hair with respect to midline of the scalp, without apparent discrepancies in length, texture, or thickness of individual hairs. Unusual findings relating to color of the scalp hair were noted in 4 of the 45 individuals (9%); 2 had focal patches of hypopigmented or depigmented scalp hair and 2 had multiple strands of depigmented hair throughout the scalp.

Table I. Hair findings in Proteus syndrome

Feature	Individuals, No. (%) (N = 45)	95% Confidence Interval (%)
Asymmetric hypertrichosis on body (nonscalp)	29 (64)	49-78
Blaschkoid hypertrichosis	16 (36)	22-51
Nonblaschkoid patches of hypertrichosis	11 (24)	13-40
Hypertrichosis of 1 limb	10 (22)	11-37
Asymmetric axillary hair density	2 (4)	1-15
Scalp hair aberrancy	11 (24)	13-40
Scattered or patchy decreased hair depigmentation	4 (9)	2-21
Focal sparsity of hair	2 (4)	1-15
Diffuse thinning or sparsity of hair atypical for age*	2 (4)	1-15
Asymmetric hair density with respect to midline	1 (2)	<0.1-12

*Observed in individuals aged 3 years and 9 years respectively.

DISCUSSION

Abnormalities of hair length, thickness, or distribution were present in most of the individuals with Proteus syndrome. The findings ranged from asymmetric hypertrichosis to irregularities in scalp hair density and color. This thorough evaluation of a large cohort establishes these abnormalities as a common manifestation of Proteus syndrome. Similar findings have been described in case reports, specifically terminal hair overlying a blaschkoid epidermal nevus,[9] discrepancy in thickness of scalp hair with respect to midline,[10] and sparsity of eyebrows.[10] In addition, unilateral hypertrichosis involving most of the body was reported in 1 individual.[11] However, the diagnosis of Proteus syndrome in these individuals was not confirmed molecularly, and many patients described in the literature do not fulfill diagnostic criteria.[12] Our observations in individuals with clinically diagnosed and molecularly confirmed Proteus syndrome establish that hair changes are a very common but underreported mosaic phenotype of Proteus syndrome.

The most common hair change that we observed was asymmetric hypertrichosis. Patches of increased hair thickness and length most commonly presented in distributions following the lines of Blaschko, although they also frequently appeared in a variety of nonblaschkoid patterns and distributions. Hypertrichotic patches were present on otherwise normal-appearing skin or in association with an epidermal nevus. The appearances of hypertrichotic epidermal nevi were highly variable, falling within a spectrum ranging from a slightly pigmented patch to a thick, verrucous, deeply pigmented plaque. In addition, a considerable number of individuals had hypertrichosis overlying most of one limb relative to the other.

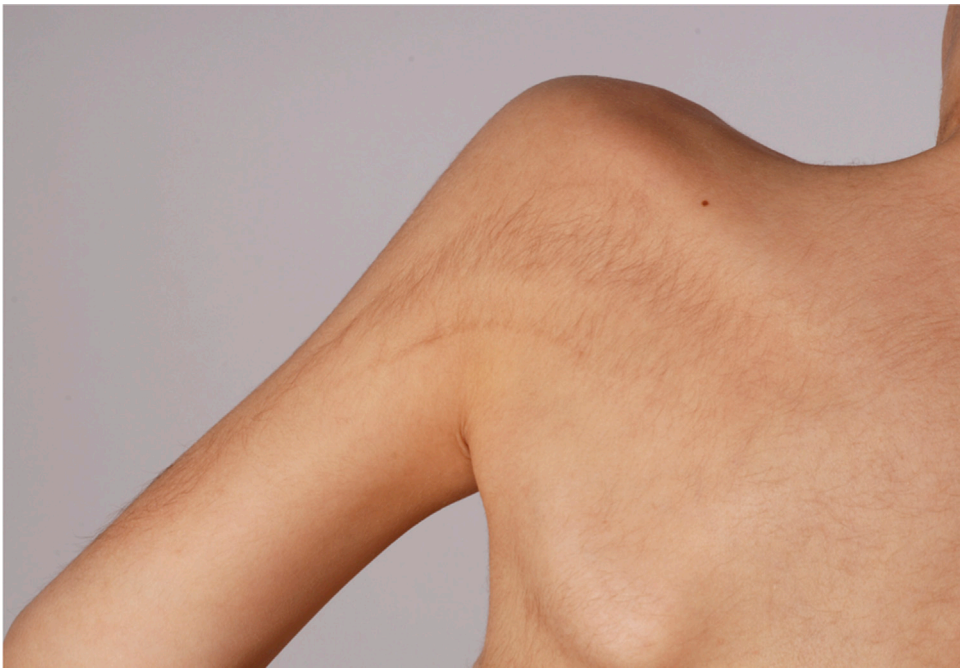

Fig 1. Linear, blaschkoid hypertrichosis on the left shoulder. Some regions of hypertrichosis show no apparent changes to the underlying skin, while others have faint hyperpigmentation.

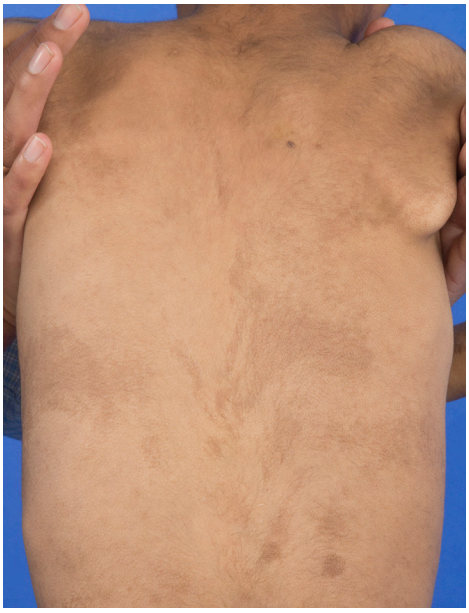

Fig 2. Hypertrichosis on the back following the distribution of Blaschko lines. The hypertrichosis overlies an epidermal nevus ranging in appearance from hyperpigmented patches to slightly elevated plaques.

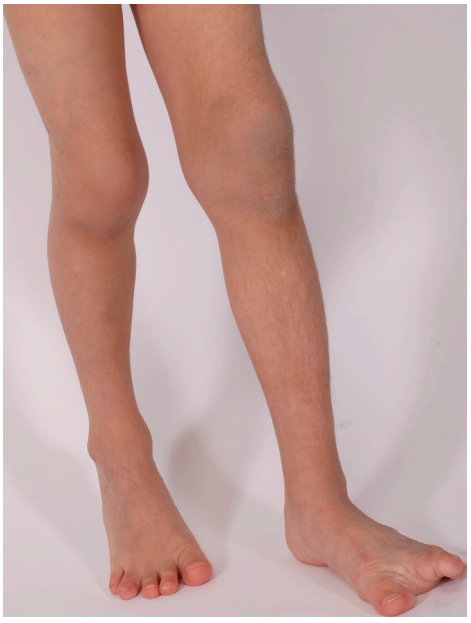

Fig 3. Overgrowth of the left leg with associated hypertrichosis.

The patterns of hypertrichosis observed in Proteus syndrome may resemble those observed in other mosaic conditions that involve the hair follicle (Table II).[13-37] Asymmetric, patchy hypertrichosis overlying otherwise normal-appearing skin resembles nevoid hypertrichosis,[13] which can have heterogeneous patterning ranging from round to checkerboard or blaschkoid.[14] In some individuals with nevoid hypertrichosis, hypertrichotic patches may additionally be associated with partial lipoatrophy,[14] a feature sometimes seen in Proteus syndrome. The differential diagnosis for hypertrichosis overlying an epidermal nevus

Table II. Mosaic conditions that involve the pilosebaceous unit

Condition	Most common genetic variant	Cutaneous lesions involving pilosebaceous unit		Other potentially associated manifestations	
		Gross appearance	Histologic features	Features relating to the skin, hair, nails, and oral mucosa	Systemic features
Nevoid hypertrichosis[13,14]	Unknown	• Well-demarcated hypertrichotic patch	• Increased density of terminal hair follicles without other pathological findings	• Hypopigmentation • Partial lipoatrophy	• Neurologic anomalies (including spina bifida) • Skeletal anomalies • Dental anomalies • Ocular anomalies
Angora hair nevus syndrome (Schauder syndrome)[15]	Unknown	• Long, soft, hypopigmented hair growing from patches of dilated hair follicles • Patches of hypopigmented, fine hair on the scalp • Blaschkoid patches of hypopigmented, fine hair on the body	• Not reported	• Hyperkeratotic, hypopigmented plaques • Koilonychia of great toes	• Craniofacial defects • Ocular anomalies • Neurologic anomalies • Skeletal anomalies
Congenital hemihypertrophy with hemihypertrichosis[16-18]	Unknown	• Unilateral corporal or limb hypertrichosis	• Increased density of terminal hair follicles without other pathologic findings	—	• Ipsilateral corporal or limb overgrowth
Becker nevus[15,19]	Somatic activating variant in *ACTB*	• Terminal hair growth overlying smooth, evenly pigmented nevus with well-demarcated border	• Increased density of terminal hair follicles • Epidermal hyperplasia • Increased melanocytes within basal layer of epidermis • Increased dermal smooth muscle bundles	—	• Undergrown ipsilateral breast or pectoralis major muscle • Ipsilateral limb hypoplasia • Scoliosis • Spina bifida
Congenital melanocytic nevus[20,21]	Somatic activating variant in *NRAS* or *BRAF*	• Terminal hair growth overlying pigmented nevus with well-demarcated border	• Increased density of terminal hair follicles • Proliferation of melanocytes within deep dermis and subcutis as well as around hair follicles, sebaceous glands, eccrine apparatus, vessel walls, and nerves	• Increased risk for melanoma	• Increased risk for leptomeningeal tumors

Continued

Table II. Cont'd

Condition	Most common genetic variant	Cutaneous lesions involving pilosebaceous unit		Other potentially associated manifestations	
		Gross appearance	Histologic features	Features relating to the skin, hair, nails, and oral mucosa	Systemic features
Congenital smooth muscle hamartoma[22-24]	Unknown	• Vellus hair growth overlying a skin-colored, or slightly hyperpigmented patch or plaque. May evolve with age into perifollicular papules that are accentuated by rubbing	• Increased density of vellus hair follicles • Proliferation of smooth muscle within dermis • Disorganized proliferation of smooth muscle within arrector pili muscle	…	…
Basaloid follicular hamartoma syndrome (Happle-Tinschert syndrome)[25,26]	Somatic variant in *SMO*	• Hypertrichosis or hypotrichosis overlying skin-colored-to-brown papules or plaques (basaloid follicular hamartomas) • Segmental acne • Patches of hypertrichosis with no gross abnormalities in underlying skin	• Anastomosing strands of basaloid cells originating from follicular infundibulum within papillary dermis, which may completely replace hair follicles	• Linear atrophoderma with hypopigmentation and hyperpigmentation	• Skeletal anomalies • Dental anomalies • Neurologic anomalies • Craniofacial anomalies • Ocular anomalies
Nevus comedonicus[15,27]	Somatic variant in *NEK9*	• Closely arranged, dilated follicular openings with keratinous plugs (resembling comedones) superimposed upon hypopigmented macules or streaks	• Dilated hair follicle ostia with hair shafts replaced by keratin layers • Occasional follicular cysts	• Milia-like lesions	• Neurologic anomalies • Ocular anomalies • Skeletal anomalies
Nevus sebaceous[15]	Somatic variant in *HRAS* or *KRAS*	• Nevus sebaceous	• Epidermal hyperplasia • Abundant sebaceous glands • Immature hair follicles • Ectopic deep dermal apocrine glands	In phacomatosis pigmentokeratotica: • Speckled lentiginous nevus • Increased risk for basal cell carcinoma and melanoma	In nevus sebaceous syndrome: • Neurologic anomalies • Ocular anomalies • Skeletal anomalies (including increased risk of vitamin D-resistant hypophosphatemic rickets) In phacomatosis pigmentokeratotica: • Neurologic anomalies • Ocular anomalies

					• Musculoskeletal anomalies (including increased risk of rhabdomyosarcoma • Endocrine anomalies • Vascular anomalies • Increased risk of nephroblastoma
Woolly hair nevus[29,38]	Somatic variant in *HRAS*	• Tightly coiled patch of hair which may be hypopigmented	• Thinning and curvature of hair follicles	• Epidermal nevi • Melanocytic nevi	• Ocular anomalies • Precocious puberty
Darier disease[30,31]	Somatic variant in *ATP2A2*	• Blaschkoid band of keratotic papules	• Keratinization of hair follicles	• White and red longitudinal bands on nails • Cobblestone-like oral mucosal lesions	• Neuropsychiatric anomalies
Incontinentia pigmenti (Bloch-Sulzberger syndrome)[32,33]	Germline (X-linked dominant lyonization) or somatic variant in *IKBKG/NEMO*	• Patchy alopecia • Patches of course hair • Sparse eyebrows and eyelashes	• Complete absence of pilosebaceous units and eccrine glands	• Erythema and blistering within first few weeks of life • Hypertrophic epidermal plaque within first few months of life • Linear hyperpigmented or vesicular lesions few months and persisting through teen years • Linear hypopigmented macules starting in late teens and persisting through adulthood • Nail dystrophy	• Dental anomalies • Neurologic anomalies • Ocular anomalies
X-linked dominant chondrodysplasia punctate (Conradi-Hunermann-Happle syndrome)[34]	Germline (X-linked dominant lyonization) variant in *EPB*	• Blaschkoid alopecia • Coarse hair • Follicular atrophoderma	• Keratotic plugs with dystrophic calcification replacing hair shaft within hair follicle	• Blaschkoid ichthyosiform erythroderma at birth	• Craniofacial anomalies • Skeletal anomalies (including short stature) • Ocular anomalies
Oral-facial-digital syndrome type I (Papillon-Léage and Psaume syndrome)[35]	Germline (X-linked dominant lyonization) variant in *ODF1*	• Blaschkoid alopecia • Coarse, brittle scalp and body hair	• Diminished hair follicles and sebaceous glands	• Geographic tongue	• Craniofacial anomalies • Renal disease • Dental anomalies

Continued

Table II. Cont'd

Condition	Most common genetic variant	Cutaneous lesions involving pilosebaceous unit		Other potentially associated manifestations	
		Gross appearance	Histologic features	Features relating to the skin, hair, nails, and oral mucosa	Systemic features
Hypohidrotic ectodermal dysplasia[36,37]	Germline (X-linked dominant lyonization) variant in *EDA* or *NEMO*	• Patchy hyperhidrosis • Hypotrichosis	• Rudimentary or absent eccrine glands • Hypertrophic apocrine glands • Reduced density of pilosebaceous units • Decreased thickness of hair shaft	--	• Dental anomalies • Immune deficiency manifesting as severe, recurrent infections

also includes Angora hair nevus syndrome, which is characterized dermatologically by long, soft, hypopigmented hair superimposed upon a blaschkoid epidermal nevus.[15] There has also been a report of an individual with multiple skeletal defects and a linear epidermal nevus containing hypertrichosis and follicular hyperkeratosis,[38] which may represent a newly described epidermal nevus syndrome.[39]

The pattern of hypertrichosis overlying a unilateral, overgrown limb is similar to that seen in congenital hemihypertrophy with hemihypertrichosis, which has been reported in 3 neonates with hypertrichosis overlying an overgrown arm and leg.[16-18] The genetic basis of each of the aforementioned disorders has yet to be identified. Given the mosaic patterning of each of these conditions and the observation here of similar features in Proteus syndrome, it is possible that mosaic variants in genes affecting the phosphoinositide 3-kinase (PI3K)-protein kinase B (AKT)-mechanistic target of rapamycin signaling pathway may be implicated.

An array of other mosaic conditions may present with involvement of hair follicles or other components of the pilosebaceous unit manifesting similarly to the phenotypes observed here. The dermatologic and extracutaneous presentations of these conditions as well as the genetic basis of each, if known, are outlined in Table II.

We postulate that the heterogeneous patterns and distributions of hypertrichosis observed within the cohort assessed may be partly attributed to occurrence of the *AKT1* variant at various times during embryogenesis within various cell lineages relevant to hair follicle development. AKT activation promotes hair follicle stem cell proliferation in the hair follicle bulge[40,41] as well as augmentation of thickness and length of hair.[42] The interfollicular epithelium and the hair follicle bulge both derive from the embryonic ectoderm, and AKT signaling has been demonstrated to induce proliferation of keratinocytes within the interfollicular epithelium.[40,43] Occurrence of the *AKT1* activating variant within ectodermal cells may account for the growth of hair overlying blaschkoid epidermal nevi. Occurrence of the variant after differentiation of the cells that generate the hair follicle bulge or interfollicular epithelium may respectively result in hypertrichosis overlying normal-appearing skin or epidermal nevi without terminal hair.

The limb bud mesenchyme, critical for development of limbs, and the dermal papilla, involved in hair follicle growth, are both derived from the mesoderm. The occurrence of the *AKT1* variant before differentiation of the limb bud mesenchyme into skin and bone lineages may

account for the co-occurrence of limb overgrowth and total limb hypertrichosis in some individuals. Further molecular study is necessary to determine whether the various patterns of hypertrichosis observed in Proteus syndrome are caused by mosaicism in distinct cell lineages.

Limitations of this study include the retrospective, observational design, omission of 6 individuals from the analysis, and lack of longitudinal follow-up for evolution of hair findings in most individuals. Surgery[44] or casting[45] have been reported antecedent to acquired localized hypertrichosis in the general population. This could have contributed to the occurrence of hypertrichosis in individuals in this study who previously underwent surgical procedures that required casting. However, the observed hypertrichosis in all individuals extended beyond the margins of surgical scars or casts. Future histologic and molecular analyses are warranted to more thoroughly elucidate the pathogenesis of hair findings observed in Proteus syndrome.

CONCLUSIONS

Unusual hair findings, particularly hypertrichosis in an asymmetric distribution, affect most individuals with a molecular diagnosis of Proteus syndrome, and they may demonstrate a previously underreported mosaic phenotype of the disorder. The findings reported here expand the scope of dermatologic findings known to be associated with Proteus syndrome.

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