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Proteus Syndrome

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Summary

Clinical characteristics

Proteus syndrome (PS) is characterized by progressive segmental or patchy overgrowth most commonly affecting the skeleton, skin, adipose, and central nervous systems. In most individuals PS has modest or no manifestations at birth, develops and progresses rapidly beginning in the toddler period, and relentlessly progresses through childhood, causing severe overgrowth and disfigurement. It is associated with a range of tumors, pulmonary complications, and a striking predisposition to deep vein thrombosis and pulmonary embolism.

Diagnosis/testing

The diagnosis of PS is established in a proband with all three general criteria (mosaic distribution of lesions, sporadic occurrence, progressive course) and a clinical score based on positive and negative criteria of at least ten points in an individual **with** a mosaic *AKT1* pathogenic variant or at least 15 points in an individual **without** a mosaic *AKT1* pathogenic variant identified by molecular genetic testing. The diagnosis of *AKT1*-related overgrowth spectrum is established in an individual **with** a mosaic *AKT1* pathogenic variant and a clinical score of 2-9.

Management

Treatment of manifestations: Management of overgrowth including orthopedic procedures to delay or halt linear bone growth; rehabilitation medicine care including physical and occupational therapy; correction of skeletal deformities such as scoliosis; dermatologic management of the skin manifestations, especially the cerebriform connective tissue nevi with pedorthic intervention as needed; surgery as needed for lipomatous overgrowth; evaluation and treatment of deep vein thrombosis and pulmonary embolism; treatment of tumors per surgeon and/or oncologist; treatment of bullous pulmonary disease per pulmonologist; developmental intervention and/or special education for developmental delays; psychosocial counseling is warranted in most individuals.

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Surveillance: Monitoring should be tailored to individual presentation. Orthopedic, rehabilitation medicine, physical therapy, occupational therapy, pulmonary, dermatology, and developmental evaluations as needed; routine monitoring for evidence of tumor development is by medical history and physical examination; periodic imaging is not indicated.

Agents/circumstances to avoid: Medications that increase the risk of deep vein thrombosis or are procoagulant; medications that increase growth (e.g., androgenic steroids, growth hormone).

Genetic counseling

PS and *AKT1*-related overgrowth spectrum are not inherited: there are no confirmed occurrences of vertical transmission or sib recurrence. There is no known risk to offspring of an affected individual; however, the number of affected individuals who have reproduced is very small. Thus, the risks to the parents of an affected child and to affected persons who do reproduce are not increased compared to the general population. Because PS and *AKT1*-related overgrowth spectrum are not inherited, prenatal testing is not indicated.

GeneReview Scope

GeneReview Scope: Included Disorders

• Proteus syndrome
  ◦ *AKT1*-related Proteus syndrome (clinical-molecular diagnosis)
  ◦ Proteus syndrome (clinical diagnosis)
• *AKT1*-related overgrowth spectrum

Diagnosis

Consensus clinical diagnostic criteria for Proteus syndrome (PS) have been published [Sapp et al 2019].

Suggestive Findings

PS **should be suspected** in a proband with the following:

- Distorting, progressive overgrowth, typically of postnatal onset, often resulting in asymmetric distortion of the skeletal architecture. Hemimegencephaly can be prenatal.
- Cerebriform connective tissue nevi characterized by deep grooves and gyrations as seen on the surface of the brain
- Linear verrucous epidermal nevus, a streaky, pigmented, rough nevus that often follows the lines of Blaschko and can be present anywhere on the body
- Adipose dysregulation, including lipomatous overgrowth and lipoatrophy
- Vascular malformations, including cutaneous capillary malformations, prominent venous patterning or varicosities, and lymphatic malformations
- Overgrowth of other tissues, most commonly spleen, liver, thymus, and gastrointestinal tract
- Tumors, most commonly meningiomas. Ovarian cystadenomas, breast cancer, parotid monomorphic adenoma, mesothelioma, and others have also been reported.
- Bullous pulmonary degeneration
- Dysmorphic facial features including dolichocephaly, long face, downslanting palpebral fissures, and/or minor ptosis, depressed nasal bridge, wide or anteverted nares, and open mouth at rest

Establishing the Diagnosis

The diagnosis of PS **is established** in a proband with **ALL** of the following **three general criteria**:

- Mosaic distribution of lesions
- Sporadic occurrence
- Progressive course

AND using the following positive (and negative) clinical criteria (see Table 1):

- A score of ≥10 points in an individual **with** a mosaic *AKT1* pathogenic variant
- A score of ≥15 points in an individual **without** a mosaic *AKT1* pathogenic variant *

Note: The diagnosis of *AKT1*-related overgrowth spectrum is established in an individual **with** a mosaic *AKT1* pathogenic variant and a score of 2-9 using clinical criteria.

* Individuals without a mosaic *AKT1* pathogenic variant should be considered to have PS, not *AKT1*-related Proteus syndrome (*AKT1*-PS). However, the clinical criteria (see Table 1) were intended to diagnose PS with confidence based only on clinical criteria, and individuals with these clinical criteria should be managed the same as those with *AKT1*-PS.

Table 1. Positive and Negative Clinical Criteria Used in the Diagnosis of Proteus Syndrome

Positive Clinical Criteria		Points
Cerebriform connective tissue nevus		**5**
Asymmetric, disproportionate overgrowth (of ≥1 of the following):	Limbs	**5**
	Hyperostosis of the skull	
	Hyperostosis of the external auditory canal	
	Megaspondylodysplasia, scoliosis, or rib hyperostosis	
Organ/visceral overgrowth (of ≥2 of the following):	Central nervous system	**5**
	Urogenital system	
	Eye	
	Spleen	
	Kidney	
	Liver	
	Tonsils or adenoids	
	Gingiva or tongue	
Bullae or cysts of the lungs		**2**
Dysregulated adipose tissue (incl ≥1 of the following):	Lipomas	**2**
	Lipodystrophy	
	Myocardial septal lipoma	
Linear verrucous epidermal nevus		**2**
Vascular malformations (incl ≥1 of the following):	Capillary malformation	**2**
	Venous malformation	
	Lymphatic malformation	
Specific tumors (incl ≥1 of the following):	Female genitourinary cystadenoma (age <11 yrs)	**1**
	Parotid monomorphic adenoma (age <11 yrs)	
	Meningioma (meningothelial & transitional subtype)	
	Testicular cystadenomas or cystadenocarcinomas	

Table 1. continued from previous page.

Positive Clinical Criteria		Points
Facial phenotype (≥3 features)	Dolichocephaly	**2**
	Long face	
	Downslanting palpebral fissures &/or minor ptosis	
	Low nasal bridge	
	Wide or anteverted nares	
	Open mouth at rest	
Deep vein thrombosis &/or pulmonary embolism		**2**
Negative Clinical Criteria		
Substantial prenatal extracranial overgrowth		**−5**
Ballooning overgrowth		**−5**

Molecular Genetic Testing

Molecular approaches can include a combination of **gene-targeted testing** (targeted analysis, single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with suggestive findings of PS and/or clinical criteria ≥10 points are likely to be diagnosed using gene-targeted testing (see **Option 1**), whereas those with a phenotype indistinguishable from many other overgrowth disorders are more likely to be diagnosed using genomic testing (see **Option 2**).

Option 1

Targeted analysis for *AKT1* pathogenic variant c.49G>A (p.Glu17Lys) in the affected tissue, if possible, can be performed first.

Note: (1) Identification of an *AKT1* pathogenic variant requires analysis of affected tissues, typically a punch biopsy of an affected area of skin. Because all *AKT1* pathogenic variants reported to date are somatic and mosaic, more than one tissue sample may be required for diagnosis. (2) Only two affected individuals are known to have an *AKT1* pathogenic variant identified in a peripheral blood sample. Therefore, the absence of a pathogenic variant in a peripheral blood sample is not sufficient to exclude the diagnosis and molecular genetic testing of DNA from affected tissue is strongly recommended.

Single-gene testing. Sequence analysis of *AKT1* may be considered. Typically, if no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications; however, to date such variants have not been identified as a cause of this disorder.

A multigene panel that includes *AKT1* and other genes of interest (see Differential Diagnosis) may be considered to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4)

Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

When the phenotype is indistinguishable from many other overgrowth disorders, **comprehensive genomic testing** does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Note: The methodology used for testing must be designed to detect mosaic variants (variant allele fraction <50%). Some individuals with *AKT1*-PS have a variant allele fraction <1%, which can be challenging (or impossible) to detect with some assay techniques.

Table 2. Molecular Genetic Testing Used in Proteus Syndrome

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
AKT1	Targeted analysis for c.49G>A (p.Glu17Lys)	~50% [3]
	Sequence analysis [4]	See footnote 5.
	Gene-targeted deletion/duplication analysis [6]	1 reported [7]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Somatic mosaicism for the *AKT1* c.49G>A variant is the most common pathogenic variant identified to date in individuals with clinically confirmed *AKT1*-related Proteus syndrome [Lindhurst et al 2011].
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
5. *AKT1* sequence analysis can identify the most common *AKT1* pathogenic variant identified in individuals with Proteus syndrome, c.49G>A (p.Glu17Lys); an additional *AKT1* pathogenic variant, c.49_50delinsAG (p.Glu17Arg), has been identified on sequence analysis in two individuals with Proteus syndrome [Buser et al 2020; Biesecker, unpublished observation].
6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
7. To date, an *AKT1* duplication including exons 3-15 was described in one infant with Proteus syndrome [AlAnzi et al 2021].

Clinical Characteristics

Clinical Description

Proteus syndrome (PS) displays a wide range of severity. Some individuals are minimally affected, but others are quite severely affected. Among the individuals in the NIH *AKT1*-related Proteus syndrome (*AKT1*-PS) cohort, there was a projected 25% mortality before age 20 years [Sapp et al 2017].

Most affected individuals have few or no manifestations at birth. Most typically, the first manifestations of the disorder occur between age six and 18 months with the onset of asymmetric overgrowth; it is most commonly of the feet or hands but may occur anywhere. An exception is that a few individuals (probably <5%) first manifest PS with hemimegencephaly, often associated with central nervous system migration defects and later intellectual disability. This manifestation is prenatal. There is a single individual reported with prenatal diagnosis of

generalized overgrowth, but this presentation is distinctly unusual [Abell et al 2020]. In most other affected individuals, the congenital manifestations are so subtle as to be discounted or missed. These include subtle degrees of asymmetry or faint linear nevi.

Overgrowth. The overgrowth in PS can be startling in its severity and rapidity of progression in contrast to most segmental overgrowth disorders. The overgrowth in individuals with PS is, for most parts of the skeleton (except congenital hemimegencephaly), absent or minimal at birth, does not typically manifest until age six to 18 months, and has had its onset as late as age 12 years. The typical progression of an area of overgrowth in an individual with PS is 15% larger at age one year, 30% larger at three years, and 100% larger at age six years. On plain radiographs the bones affected by PS, especially the tubular bones of the limbs, the vertebral bodies, and the skull, develop distorting, bizarre, irregular calcified overgrowth that can render the bone unrecognizable with time. The rapid and severe nature of the overgrowth poses a challenge to orthopedic management. It is not uncommon for the overgrowth to accelerate rapidly in childhood, with leg length discrepancies of 20 cm being reported. Scoliotic curves of more than 90 degrees are not uncommon. Any bone can be affected.

Many individuals with PS have (often unilateral) overgrowth of the tonsils/adenoids. Splenic overgrowth and asymmetric enlargement of the kidneys and testes are also not uncommon in individuals with PS.

Dermatologic findings. Cerebriform connective tissue nevi (CCTN) are present in most individuals with PS and are nearly pathognomonic. CCTN are rarely present in infancy, typically developing in childhood and progressing through adolescence. They are most commonly found on the sole, hand, alae, ear, and lacrimal puncta. CCTN are firm and have a distinct pattern resembling the brain's sulci and gyri (hence the term "cerebriform"). They should not be confused with prominent plantar or palmar wrinkling seen in other forms of overgrowth (see Sapp et al [2007] for photographic examples of lesions with similar appearance to CCTN). CCTN rarely progress in adulthood [Beachkofsky et al 2010]. The sulci of CCTN often become deep enough in late adolescence to pose challenges with cleanliness and malodor.

Linear verrucous epidermal nevi are streaky, pigmented, rough nevi that often follow the lines of Blaschko. They can be present anywhere on the body. They are most commonly recognized in the first months of life and are generally stable over time [Twede et al 2005].

Less common dermatologic findings include hypertrichosis or acne in patterns that follow the lines of Blaschko [Cartron et al 2020, Pithadia et al 2021]. These dermatologic findings are relatively specific for PS and can be useful in clinical diagnosis.

Overgrowth of lipomatous tissue / lipoatrophy. It is common for individuals to manifest overgrowth of adipose tissue, most often in infancy. Overgrowth of adipose tissue can continue to appear in novel locations throughout childhood and into young adulthood. Similarly, many individuals with PS experience marked regional lipoatrophy, and many manifest both regional lipomatous overgrowth and lipoatrophy. Persons with PS do not have the typical ovoid, encapsulated lipomas common in the elderly, and so the term "lipoma" is technically incorrect but in wide usage. Fatty infiltration of the myocardium, particularly the intraventricular septum, has been observed in a number of children and adults with PS with no functional consequences [Hannoush et al 2015].

Vascular malformations. Many individuals with PS have cutaneous capillary malformations and prominent venous patterning or varicosities; large and complex vascular malformations affect some individuals. Vascular malformations are commonly recognized in the first months of life and are generally stable over time [Twede et al 2005]. Lymphatic vascular malformations can arise in any tissue that normally includes such vessels. These can be progressive and are often present with areas of lipomatous overgrowth, which can complicate surgical approaches to lipomas.

The most urgent and life-threatening complication of PS can be deep vein thrombosis (DVT) and pulmonary embolism (PE) [Slavotinek et al 2000]. Individuals with DVT can present with a palpable subcutaneous rope-like mass, swelling, erythema, pain, and distal venous congestion. Symptoms of PE include shortness of breath, chest pain, and cough, which may include hemoptysis. The rarity of DVT and PE in the general pediatric population can result in a delay in diagnosis.

Those with PS manifest skeletal and other overgrowth in areas where no vascular malformations are present (unlike some other overgrowth conditions).

Importantly, arteriovenous malformation (AVM) is uncommon in PS.

Pulmonary venous dilatation on chest imaging is common [Mirmomen et al 2021]. Other chest imaging findings can include bullae, fibrotic lesions, and masses.

Tumors, most of which are benign, observed in multiple individuals include meningiomas and ovarian cystadenomas. A number of other tumors have been seen in individuals with PS. It is presumed that PS causes a modest but significant increase in many types of tumors, in contrast to other syndromes that are associated with a very specific subset of tumors. Some of these tumors (especially the ovarian tumors) can exhibit borderline histology with attributes of both benign and malignant lesions. These must be evaluated thoroughly by experts with knowledge of both gynecologic malignancy and Proteus hyperplasia.

Bullous pulmonary disease is uncommon but does affect some individuals with PS [Lim et al 2011], most commonly in late childhood or adolescence. As with other disease manifestations, this can progress with startling rapidity. It commonly manifests by reduced exercise tolerance or as an incidental finding from chest imaging. This can be identified by pulmonary scarring and hyperlucencies on pulmonary imaging [Mirmomen et al 2021].

Dysmorphic facial features typically evolve during childhood and are not obvious at birth. Reported facial features include dolichocephaly, long face, downslanting palpebral fissures, and/or minor ptosis, depressed nasal bridge, wide or anteverted nares, and open mouth at rest.

Gynecologic manifestations. Several individuals have been described with severe, complex overgrowth of the uterus, cervix, and ovaries that can be difficult to distinguish from malignancy [Leoni et al 2019; Severino-Freire et al 2019; Biesecker, unpublished observations].

Psychosocial issues. In addition to functional compromise, the skeletal and connective tissue overgrowth of PS can result in disfigurement for some individuals, a significant concern for many families [Turner et al 2007]. This condition is progressive, and the degree of severity varies widely among individuals, creating uncertainty for both clinicians and families. Coping with an ultra-rare and chronic condition like PS poses challenges for many individuals and families.

Prognosis is based on the location and degree of the overgrowth present in the individual and the presence or absence of significant complications such as bullous pulmonary disease, hemimegencephaly, and PE. The disorder is highly variable. While it is difficult to calculate average life expectancy, it is clear that there are many more children with PS than adults. With appropriate management, mildly affected individuals have an excellent prognosis.

AKT1-Related Overgrowth Spectrum

Because PS is a mosaic disorder, it is axiomatic that there will be substantial interindividual phenotypic variation because every affected individual has the causative variant in a distinct spectrum of their tissues. This variation is in both the nature and the severity of the manifestations. Because this spectrum of variation is continuous, any definition of minimal diagnostic criteria for the Proteus phenotype must be arbitrary. Sapp et al [2019] have

proposed a threshold in their points-based system, as described previously in the diagnostic criteria. This threshold is intended to be meaningful and useful to clinicians, but the distinction should not be exaggerated. Affected individuals above and below these thresholds can have serious complications of the disease, and each must be evaluated as an individual with a monitoring and treatment plan appropriate to their individual manifestations.

Genotype-Phenotype Correlations

All but two individuals with *AKT1*-PS are known to have the same, mosaic pathogenic variant (p.Glu17Lys) in *AKT1*. Two individuals are instead known to have a mosaic c.49_50delinsAG (p.Glu17Arg) variant [Buser et al 2020; Biesecker, unpublished observation]. A detailed autopsy study of an individual with the common p.Glu17Lys variant showed that while there was an overall correlation of variant allele fraction levels with the presence of gross or histologic manifestations of overgrowth (hypertrophy or hyperplasia), this correlation was not absolute [Doucet et al 2016]. Some tissues with overgrowth had no detectable variant, while other apparently unaffected tissues did contain the variant. Clinicians should be cautious when assuming that a tissue or organ is unaffected by PS.

Penetrance

Incomplete penetrance cannot be assessed in a practical way in a mosaic genetic disorder that is not inherited. As it has been shown that unaffected tissues can contain the causative variant, it is theoretically possible that an individual with lower variant allele fraction levels could be asymptomatic. This is mainly of academic interest, as it is difficult to imagine a circumstance where this would be sought and detected.

Nomenclature

Other descriptors used include elephant man disease. This descriptor is derived from the fact that Mr Joseph Carey Merrick, who held this unfortunate descriptor, is now thought to have had PS [Cohen 1987]. The use of this descriptor for other than historical purposes is discouraged.

Prevalence

PS is very rare. The prevalence is difficult to measure, but approximately 100 individuals are known to the author [L Biesecker, personal observation]. A very rough estimate is that PS affects 1:1,000,000-10,000,000 persons.

Genetically Related (Allelic) Disorders

The only other phenotypes associated with somatic pathogenic variants in *ATK1* are tumors (primarily breast tumors) where a small minority of such tumors have the *AKT1* p.Glu17Lys somatic pathogenic variant and a rare lesion termed sclerosing pneuomocytoma that, like Proteus syndrome overgrowth, lies on a spectrum between benign and malignant lesions [Boland et al 2021].

It is hypothesized that a germline *AKT1* p.Glu17Lys or p.Glu17Arg pathogenic variant would be lethal in early development [Happle 1986]. Animal data show that an embryo with a germline *Akt1* p.Glu17Lys pathogenic variant would have early embryonic lethality [Lindhurst et al 2020].

Differential Diagnosis

Significant diagnostic confusion regarding Proteus syndrome (PS) exists. Although the following disorders share some features with PS, both the natural history (i.e., almost always postnatal onset) and manifestations (e.g., disproportionate and progressive distorting skeletal overgrowth, cerebriform connective tissue nevi) of PS are important distinctions that can aid in clinical diagnosis.

***PTEN* hamartoma tumor syndrome (PHTS)** is a heterogeneous disorder that manifests asymmetric overgrowth, macrocephaly, cutaneous vascular malformations, and tumor susceptibility. The full spectrum of this interesting and distinctive disorder is not known, but it can be readily distinguished from PS. A phenotypic subtype, Cowden syndrome, is the consequence of a germline pathogenic variant in *PTEN* with a somatic, mosaic second *PTEN* variant that gives the phenotype its segmental attributes.

PHTS includes growth abnormalities with linear nevi and vascular malformations that are clinically and molecularly distinct from those of PS.

PHTS is inherited in an autosomal dominant manner; PS is not inherited. Thus, the genetic implications in the two disorders are quite distinct, providing further argument for a clear distinction between individuals affected with PS and those with PHTS.

***PIK3CA*-related overgrowth spectrum** encompasses a range of clinical findings in which the core features are congenital or early-childhood onset of segmental/focal overgrowth with or without cellular dysplasia in the absence of a family history of similarly affected individuals (i.e., single occurrence in a family). Clinical syndromes in the *PIK3CA*-related overgrowth spectrum include:

- **CLOVES syndrome** (*c*ongenital *l*ipomatous asymmetric *o*vergrowth of the trunk, lymphatic, capillary, venous, and combined-type *v*ascular malformations, *e*pidermal nevi, *s*keletal and *s*pinal anomalies] syndrome) manifests prenatal asymmetric overgrowth that is primarily proportionate in nature. Affected persons commonly have splayed feet and toes. The vascular malformations are most commonly combined lymphatico-venous anomalies with cutaneous blebbing and weeping. The lipomatous nature of the overgrowth is characterized by overgrowth of fat within normal fatty fascial planes and linear verrucous epidermal nevi. Some persons can have central nervous system abnormalities.
- Hemihyperplasia**,** either as an isolated finding or associated with one of a variety of other manifestations (for review, see Cohen et al [2002]), should be considered in the differential diagnosis of PS. One of the more specific types of hemihyperplasia is the **hemihyperplasia with multiple lipomatosis syndrome** [Biesecker et al 1998]. This congenital, primarily non-progressive form of hemihyperplasia is sometimes confused with PS. This entity is also now best considered part of the *PIK3CA*-related overgrowth spectrum.
- **Klippel-Trenaunay syndrome** is a disorder that manifests both overgrowth and vascular malformations. However, in this disorder the overgrowth is generally ipsilateral and overlapping with the vascular malformations, the typical vascular malformation is the lateral venous anomaly, and the skeletal overgrowth is entirely lacking in the distortion and progressivity seen in persons with PS [Uller et al 2014]. This entity is also now best considered part of the *PIK3CA*-related overgrowth spectrum.

PIK3CA-related overgrowth spectrum is caused by a heterozygous mosaic (or, rarely, constitutional) activating pathogenic variant in *PIK3CA*. No confirmed vertical transmission or sib recurrence has been reported to date.

Management

No clinical practice guidelines for Proteus syndrome (PS) have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with Proteus syndrome (PS), the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended [Tosi et al 2011].

Table 3. Proteus Syndrome: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Musculoskeletal	• Detailed & comprehensive orthopedic eval (incl general, spine, & limbs) • Skeletal survey as baseline study of extent & severity of overgrowth	
	CT exam, possibly w/3D reconstruction, for persons w/ significant scoliosis	As vertebral bodies are commonly progressively deformed, this study can be very helpful for surgical planning.
	Rehab medicine eval	Incl assessment for custom footwear & orthotics to address functional consequences of overgrowth
Pulmonary	• Pulmonology consultation • Pulmonary function testing	
	High-resolution CT exam of chest	For those w/signs or symptoms suggestive of bullous pulmonary disease
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech-language eval • Eval for early intervention / special education
Other	Other imaging techniques (e.g., CT, MRI, US) should be considered based on clinical findings.	
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of PS to facilitate medical & personal decision making
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.	

MOI = mode of inheritance; PS = Proteus syndrome; US = ultrasound
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

PS is a complex multisystem disorder and individuals benefit from a coordinated and multidisciplinary clinical approach tailored to the individual's specific needs and manifestations (see Table 4).

Table 4. Proteus Syndrome: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Skeletal overgrowth	• Mgmt per orthopedist • Epiphysiostasis & epiphysiodesis for overgrowth of tubular bones [1]	One intervention that the authors have found to be detrimental to persons w/PS is distraction osteotomy (Ilizarov procedure) performed on the normal (shorter) limbs. [2]
	• Mgmt by rehab medicine, incl PT & OT • Custom-designed footwear or orthotics due to leg-length inequality	The skeletal overgrowth of PS can result in significant biomechanical & functional compromise.

Table 4. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Scoliosis	• Referral to orthopedist if scoliosis is identified on clinical &/or radiographic exam • Frequent monitoring due to risk of rapid progression [2] • Surgery is often indicated, as progressive nature of scoliosis can lead to fatal restrictive lung disease.	Scoliosis surgery is high risk in persons w/PS; DVT & PE have led to death even w/ prophylactic anticoagulation. [3]
CCTN	• Mgmt by dermatologist • Monitor for pressure ulcerations & malodor (due to difficulty w/cleanliness of deepening sulci in late adolescence) • Pedorthic referral as needed for issues w/shoe fit	Surgical removal of CCTN has been successfully accomplished in ≥2 persons.
Overgrowth of lipomatous tissue / lipoatrophy	Open surgical approaches are preferred to liposuction because highly vascularized lipomatous overgrowth in some persons can result in difficult-to-control hemorrhaging &/or chronically weeping lymphatics. [1]	Mgmt is challenging because areas of adipose overgrowth are not encapsulated & discrete (in contrast to lipomas), can be difficult to resect, & commonly regrow after surgical debulking.
DVT & PE	Emergent eval for signs/symptoms of DVT (e.g., palpable subcutaneous rope-like mass, swelling, erythema, pain, distal venous congestion) or PE (e.g., shortness of breath, chest pain, cough, hemoptysis). • **Eval for DVTs:** in absence of cardiopulmonary compromise, consider D-dimer assay &/or US eval. • **Eval of PE:** high-resolution chest CT (spiral CT) w/contrast. Ventilation-perfusion nuclear medicine scanning may be appropriate in some persons. • Treatment of DVT & PE should follow recommended anticoagulation guidelines for these disorders.	• Persons w/PE can be asymptomatic; therefore, a person w/DVT should be evaluated for PE regardless of symptoms. • Note: Hematologic consultation for consideration of anticoagulant prophylaxis for persons undergoing surgery or other procedures that may predispose to DVT/PE is recommended.
Tumors	Treatment for tumors per surgeon &/or oncologist [1]	
Bullous pulmonary disease	• Pulmonary eval for persons w/bullous pulmonary disease • Resection of large bullous lesions may be indicated in some persons. [1]	Bullous disease in context of scoliosis can pose significant & complex challenges for appropriate mgmt.
Developmental delay	Developmental & educational support incl special education as needed for those w/developmental delays.	
Psychosocial issues	Psychosocial counseling as needed	Although PS is exceedingly rare, a robust support group infrastructure exists, & many families find this very helpful (see Resources).

CCTN = cerebriform connective tissue nevi; DVT = deep vein thrombosis; OT = occupational therapy; PE = pulmonary embolism; PS = Proteus syndrome; PT = physical therapy; US = ultrasound

1. Hematologic consultation for consideration of anticoagulant prophylaxis for individuals undergoing surgery or other procedures that may predispose to DVT/PE is recommended.

2. Tosi et al [2011]

3. Authors, personal observation

Surveillance

Individualized surveillance plans for the skeletal, pulmonary, soft tissue, and other manifestations of PS should be developed according to the individual's specific needs (see Table 5).

Table 5. Proteus Syndrome: Recommended Surveillance

System/Concern	Evaluation	Frequency
Musculoskeletal	• Orthopedic eval to assess for progression of overgrowth & scoliosis • Imaging per orthopedist • Rehab medicine, PT, &/or OT eval to assess mobility issues, footwear, & orthotics needs	Annually or as needed based on progression
Pulmonary	• Pulmonary eval • Pulmonary function testing	As needed
Dermatology	Dermatology assessment	
Development	Developmental assessment	
Tumors	• Directed medical history & exam w/primary care clinician for signs/symptoms of malignancy (e.g., pain, unexpected growths, signs of obstruction or compression) • Imaging as needed for signs/symptoms concerning for tumor(s); periodic imaging is not indicated.	Every 6-12 mos

OT = occupational therapy; PT = physical therapy

Agents/Circumstances to Avoid

Medications that increase the risk of deep vein thrombosis or are procoagulant should be avoided.

Medications that increase growth (e.g., androgenic steroids, growth hormone) should be avoided.

Evaluation of Relatives at Risk

Because PS is not inherited, relatives are not at increased risk and do not require evaluation for recurrence of this condition. Every individual has the same likelihood of having a somatic mutation that could cause Proteus syndrome, irrespective of whether they are related to someone with Proteus syndrome or not.

Pregnancy Management

There are no data on the management of pregnancy in women with PS. Pregnancy presents theoretic risks, especially the risk of thrombosis of the pelvic veins.

Therapies Under Investigation

A pilot Phase 0/I pharmacodynamic study of miransertib (formerly ARQ-092) has been completed and showed a favorable safety profile with some suggestions of efficacy [Keppler-Noreuil et al 2019]. One of the six individuals in that trial perceived clinical benefit and elected to continue therapy and has been reported in long-term follow up after five years of treatment with continuing benefit [Ours et al 2021]. Currently, a Phase II efficacy trial is under way and recruiting individuals for participation (NCT04316546).

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Proteus syndrome (PS) and *AKT1*-related overgrowth spectrum are not inherited.

- There are no confirmed occurrences of vertical transmission or sib recurrence.
- The molecular data show that all persons with a molecular diagnosis are mosaic for *AKT1* pathogenic variants c.49G>A or c.49_50delinsAG or an *AKT1* duplication including exons 3-15, suggesting that mutation occurred post fertilization in one cell of the multicellular embryo.

Risk to Family Members

Parents of a proband. No parent of a child meeting diagnostic criteria for PS or *AKT1*-related overgrowth spectrum has been demonstrated to have any significant, distinctive manifestations of PS or *AKT1*-related overgrowth spectrum, nor would such a finding be expected, given the somatic mutational mechanism of the disorders. All fetuses would appear to be at the same risk of having such a mutational event, irrespective of their family history of PS.

Sibs of a proband. Given the somatic mutational mechanism of PS and *AKT1*-related overgrowth spectrum, the risk for an affected sib would be expected to be the same as in the general population.

Offspring of a proband. The reproductive outcome data on adults with PS and *AKT1*-related overgrowth spectrum are very limited. There are no instances of vertical transmission of PS or *AKT1*-related overgrowth spectrum.

Other family members. The risk to other family members is the same as that in the general population.

Related Genetic Counseling Issues

Family planning

- Counseling for recurrence risks in PS and *AKT1*-related overgrowth spectrum should emphasize that, while no pregnancy is at zero risk, all evidence suggests that the risk of recurrence for these disorders is not increased compared to the general population.
- The optimal time for determination of genetic risk is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected.

Prenatal Testing and Preimplantation Genetic Testing

Family history of Proteus syndrome or *AKT1*-related overgrowth spectrum. As PS and *AKT1*-related overgrowth spectrum are not inherited, molecular genetic prenatal testing and preimplantation genetic testing are not indicated.

No family history of Proteus syndrome or *AKT1*-related overgrowth spectrum. Prenatal testing for a mosaic *AKT1* pathogenic variant may be considered if hemimegencephaly – a feature associated with prenatal-onset atypical PS – is incidentally observed on ultrasound examination [Abell et al 2020]. Note that there are a number of published reports of prenatal hemimegencephaly, but most individuals reported had a diagnosis other than PS (most commonly *PIK3CA*-related overgrowth spectrum).

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **MedlinePlus**
  Proteus syndrome
- **Proteus Foundation**
  www.proteus-syndrome.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Proteus Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
AKT1	14q32.33	RAC-alpha serine/threonine-protein kinase	AKT1 database	AKT1	AKT1

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Proteus Syndrome (View All in OMIM)

164730	AKT SERINE/THREONINE KINASE 1; AKT1
176920	PROTEUS SYNDROME

Molecular Pathogenesis

The PI3KCA/AKT pathway includes a number of other gene products that have been implicated in oncogenesis and/or overgrowth. This pathway is a key mediator of signal transduction from receptor tyrosine kinase growth-promoting and apoptosis-inhibiting factors. In addition to *AKT1*:

- *AKT2* pathogenic variants cause adipose dysregulation and hypoglycemia [Hussain et al 2011].
- *AKT3* pathogenic variants cause hemimegencephaly [Poduri et al 2012].
- *PTEN* pathogenic variants (the best known) are known to cause both Cowden syndrome and segmental overgrowth phenotypes that overlap with, but are clinically distinct from, Proteus syndrome (PS), namely type 2 segmental Cowden syndrome or SOLAMEN syndrome [Caux et al 2007].
- *PIK3CA* pathogenic variants have been demonstrated in a wide range of clinically diverse overgrowth syndromes including CLOVES syndrome, [Kurek et al 2012] a phenotype termed fibroadipose overgrowth [Lindhurst et al 2012], isolated macrodactyly, hemihyperplasia, Klippel-Trenaunay syndrome, and others. See *PIK3CA*-Related Overgrowth Spectrum and Keppler-Noreuil et al [2014].

It has been shown that *AKT1* pathogenic variant p.Glu17Lys causes constitutive activation of the AKT1 kinase by means of pathologic localization to the plasma membrane and activation of the PI3KCA/AKT pathway [Carpten et al 2007].

Mechanism of disease causation. Gain of function

***AKT1*-specific laboratory technical considerations.** The methodology used for testing must be designed to detect mosaic variants. Some individuals with *AKT1*-related Proteus syndrome have had variant allele frequencies below 1%, which can be challenging (or impossible) to detect with some assay techniques. The tissue selection is critical for success. Tissues that are clearly clinically affected (e.g., linear verrucous epidermal nevi or cerebriform connective tissue nevus) are more likely to have a significant variant allele frequency. It is strongly recommended to not use peripheral blood for molecular genetic testing in individuals with suspected PS.

Table 6. Notable *AKT1* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_005163.2 NP_005154.2	c.49G>A	p.Glu17Lys	Most common pathogenic variant identified in persons w/*AKT1*-PS
	c.49_50delinsAG	p.Glu17Arg	Observed in 2 persons to date

AKT1-PS = *AKT1*-related Proteus syndrome
Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Chapter Notes

Author Notes

Leslie G Biesecker, MD, is a board-certified clinical geneticist and pediatrician. He performs clinical and molecular research on Proteus syndrome (PS) and related disorders at the NIH.

Leslie G Biesecker, Christopher Ours, and Julie Sapp are actively involved in clinical research regarding individuals with *AKT1*-related Proteus syndrome (*AKT1*-PS). They would be eager to communicate with persons who have any questions regarding diagnosis of *AKT1*-PS, especially for individuals who may be eligible for the Phase II clinical trial (NCT04316546) or other considerations.

Leslie G Biesecker, Christopher Ours, and Julie Sapp are also interested in hearing from clinicians treating families affected by PS in whom no causative variant has been identified through molecular genetic testing of appropriate tissues for *AKT1* variants.

Contact Leslie G Biesecker to inquire about review of *AKT1* variants of uncertain significance.

Revision History

- 25 May 2023 (sw) Comprehensive update posted live
- 10 January 2019 (lgb) Revision: Category C criteria corrected (added bullous pulmonary degeneration)
- 4 January 2018 (sw) Comprehensive update posted live
- 9 August 2012 (me) Review posted live
- 19 April 2012 (lgb) Original submission

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