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Proteus Syndrome

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Summary

Clinical characteristics

Proteus syndrome is characterized by progressive segmental or patchy overgrowth most commonly affecting the skeleton, skin, adipose, and central nervous systems. In most individuals Proteus syndrome 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 Proteus syndrome is based on clinical criteria that include all three general characteristics (mosaic distribution of lesions, sporadic occurrence, progressive course) and additional specific clinical criteria. Identification of a mosaic, somatic, heterozygous pathogenic variant in *AKT1* by molecular genetic testing can establish the diagnosis if the clinical criteria are inconclusive.

Management

Treatment of manifestations: Management of overgrowth is the chief concern; the approaches are diverse and include various 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; monitoring for and treating deep vein thrombosis and pulmonary embolism; monitoring and treating bullous pulmonary disease; developmental intervention or special education for developmental delays; psychosocial counseling is warranted in most instances.

Surveillance: Monitoring should be tailored to individual presentation; routine monitoring for evidence of tumor development is by medical history and physical examination; periodic imaging is not indicated.

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

Genetic counseling

All individuals with clinically confirmed Proteus syndrome known to these authors have been simplex occurrences caused by somatic mosaicism for the specific *de novo* pathogenic variant c.49G>A (p.Glu17Lys). It is hypothesized that a non-mosaic (i.e., germline) *AKT1* c.49G>A pathogenic variant would be lethal in early development. 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 Proteus syndrome is not inherited, prenatal testing is not indicated.

Diagnosis

Suggestive Findings

Proteus syndrome (PS) **should be suspected** in a proband with the following.

Major findings

- Distorting, progressive overgrowth, typically of postnatal onset often resulting in asymmetric distortion of the skeletal architecture. Hemimegencephaly can be prenatal.
- Cerebriform connective tissue nevi (CCTN), a specific type of connective tissue nevus that is characterized by deep grooves and gyrations as seen on the surface of the brain
- Linear verrucous epidermal nevus (LVEN), 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
- Other:
  - 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 Proteus syndrome (PS) **is established** in a proband with the following **general** and **specific** criteria. Identification of a mosaic, somatic, heterozygous pathogenic variant in *AKT1* by molecular genetic testing (see Table 1) can establish the diagnosis if clinical criteria are inconclusive.

- ALL of the following **general** criteria:
  - Mosaic distribution of lesions
  - Sporadic occurrence
  - Progressive course

  AND
- **Specific** criteria from categories A-C:

- One from category A; OR
- Two from category B; OR
- Three from category C

Categories of Specific Criteria to Establish the Diagnosis of Proteus Syndrome

Category A. Cerebriform connective tissue nevus (CCTN). See Suggestive Findings.

Category B

- Linear epidermal nevus
- Asymmetric, disproportionate overgrowth (≥1 of the following):

  Note: Asymmetric, disproportionate overgrowth should be carefully distinguished from asymmetric, proportionate, or ballooning overgrowth.
  - Limbs
  - Hyperostosis of the skull
  - Hyperostosis of the external auditory canal
  - Megaspondylodysplasia (i.e., abnormal growth of vertebrae)
  - Viscera: spleen/thymus
- Specific tumors with onset before the second decade (either of the following):
  - Bilateral ovarian cystadenoma
  - Parotid monomorphic adenoma

Category C

- Dysregulated adipose tissue (either of the following):
  - Lipomatous overgrowth
  - Regional lipoatrophy
- Vascular malformations (one of the following):
  - Capillary malformation
  - Venous malformation
  - Lymphatic malformation
- Bullous pulmonary degeneration
- Facial phenotype (all of the following):
  - Dolichocephaly
  - Long face
  - Downslanting palpebral fissures and/or minor ptosis
  - Depressed nasal bridge
  - Wide or anteverted nares
  - Open mouth at rest

Molecular Genetic Testing

Approaches can include **targeted analysis**, use of a **multigene panel**, and **more comprehensive genomic testing**:

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

Note: (1) Although a single *AKT1* variant has been reported, it is possible that other variants in this gene detectable by sequence analysis could be causative of disease. (2) Because all *AKT1* c.49G>A pathogenic variants reported to date are somatic and mosaic, more than one tissue sample may be required for diagnosis. Identification of an *AKT1* pathogenic variant requires analysis of affected tissues, typically a punch biopsy of an affected area of skin. (3) A minority of affected individuals (2/31 reported by Lindhurst et al [2011]) with the *AKT1* c.49G>A pathogenic variant identified in one or more tissues had the 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.

- **A multigene panel** that includes *AKT1* and other genes of interest (see Differential Diagnosis) may be considered. 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*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition at the most reasonable cost while limiting identification of pathogenic variants in genes that do not explain the underlying phenotype. (3) 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.

- **More comprehensive genomic testing** (when available) including exome sequencing and genome sequencing may be considered. Such testing may provide or suggest a diagnosis not previously considered (e.g., a variant in a different gene or genes that results in a similar clinical presentation).

  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: that is, variants at a less than 50% allelic level. Some individuals with PS have had variant allele frequencies below 1%, which can be challenging (or impossible) to detect with some assay techniques.

Table 1. Molecular Genetic Testing Used in Proteus Syndrome

Gene [1]	Test Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by This Method
AKT1	Targeted analysis	33/70 [3, 4]
	Sequence analysis [4]	See footnote 5
	Gene-targeted deletion/duplication analysis [6]	Unknown [7]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Somatic mosaicism for the *AKT1* c.49G>A variant is the only pathogenic variant identified to date in individuals with clinically confirmed PS [Lindhurst et al 2011].
4. The c.49G>A variant can be detected by sequence analysis of the surrounding region. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. 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. Although a single *AKT1* variant has been reported, it is possible that other variants in this gene detectable by sequence analysis could be causative of disease.
6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include: quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. No data on detection rate of gene-targeted deletion/duplication analysis are available.

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 PS cohort, there was a projected 25% mortality before the age of 20 years [Sapp et al 2017].

Most affected individuals have little 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 (probably <5%) first manifest PS with hemimegencephaly, often associated with CNS migration defects and later intellectual disability. This manifestation is prenatal. 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° 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. CCTNs 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. True CCTNs 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 a CCTN). CCTNs rarely progress in adulthood [Beachkofsky et al 2010]. The sulci of CCTNs commonly get 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].

Overgrowth of lipomatous tissue / lipoatrophy. It is common for individuals to manifest overgrowth of adipose tissue, most commonly 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 intraventicular 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.

Tumors, most of which are benign. Tumors observed in multiple individuals include meningiomas, ovarian cystadenomas, and parotid monomorphic adenomas. A number of other tumors have been seen in individual patients 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.

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.

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.

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 pulmonary embolism. The disorder is highly variable. While it is difficult to calculate 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.

Genotype-Phenotype Correlations

PS is known to be caused by only a single, mosaic pathogenic variant (p.Glu17Lys) in *AKT1*. A detailed autopsy study [Doucet et al 2016] of an individual showed that while there was an overall correlation of variant levels with the presence of gross or histologic manifestations of overgrowth (hypertrophy or hyperplasia), this correlation was not tight nor absolute. Some tissues with overgrowth had no detectable variant, while other apparently unaffected tissues did harbor the variant. Clinicians should be cautious when assuming that a tissue or organ is unaffected by this disease.

Penetrance

Incomplete penetrance cannot be assessed in a mosaic genetic disorder that is not inherited.

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 – 1:10,000,000 persons.

PS is pan ethnic.

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.

It is hypothesized that a germline *AKT1* p.Glu17Lys pathogenic variant would be lethal in early development [Happle 1986]. Animal data suggest that an embryo with a germline *AKT1* p.Glu17Lys pathogenic variant would have early embryonic lethality, if such gametes are capable of leading to a fertilized embryo.

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, CCTN) 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, described as type II segmental Cowden syndrome [Happle 2007] or SOLAMEN syndrome [Caux et al 2007], is the consequence of a germline pathogenic variant in *PTEN* with a somatic, mosaic second *PTEN* variant that gives the phenotype its segmental attributes.

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

PTHS 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 PTHS.

CLOVE(S) 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) is one of several now-distinct entities previously included in the heterogeneous designation of PS [Sapp et al 2007]. It 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 CNS abnormalities. See *PIK3CA*-Related Segmental Overgrowth.

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. 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.

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].

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with Proteus syndrome (PS), the following evaluations are recommended if they have not already been completed [Tosi et al 2011]:

- Detailed and comprehensive (general, spine, and hand) orthopedic evaluation
- Skeletal survey as a baseline study of the extent and severity of overgrowth
- CT examination, possibly with three-dimensional reconstruction for individuals with significant scoliosis. As the vertebral bodies are commonly progressively deformed, this study can be very helpful for surgical planning.
- Pulmonology consultation, pulmonary function testing, and high-resolution CT examination of the chest for individuals with signs or symptoms suggestive of bullous pulmonary disease
- Neurodevelopmental evaluation for those with developmental delays
- Consultation with a clinical geneticist and/or genetic counselor
- Rehabilitation medicine evaluation, including fabrication of custom footwear and orthotics to address functional consequences of overgrowth

Other imaging techniques (e.g., CT, MRI, and ultrasound examinations) are highly useful and should be determined by manifestations on examination and by the medical history.

Treatment of Manifestations

As with any complex and multisystem disorder, individuals with PS benefit from a coordinated and multidisciplinary clinical approach tailored to the individual's specific needs and manifestations.

Overgrowth is an ongoing issue for many individuals with PS. The management is complex and highly dependent on the nature of the overgrowth, which can vary substantially.

For overgrowth of tubular bones, epiphysiostasis and epiphysiodesis should be the mainstays of management. One intervention that the authors have found to be detrimental to individuals with PS is distraction osteotomy (so-called Ilizarov procedure) performed on the normal (shorter) limbs. Readers are referred to a review and conference report for more details on this complex issue [Tosi et al 2011].

The skeletal overgrowth of PS can result in significant biomechanical and functional compromise. Because of this, ongoing and comprehensive rehabilitation medicine care, including physical and occupational therapy, is important for many individuals. In addition, many individuals with PS develop substantial needs for custom-designed footwear or orthotics due to leg-length inequality or plantar CCTNs.

Refer to an orthopedist if scoliosis is identified on clinical and/or radiographic examination. Scoliosis surgery is high-risk in individuals with PS. The authors are aware of individuals who have died from DVT and PE, with prophylactic anticoagulation. In spite of this risk, such surgery is indicated because the progressive nature of the scoliosis can lead to fatal restrictive lung disease. Scoliosis in individuals with PS can advance extremely rapidly, and attentive and frequent monitoring is warranted [Tosi et al 2011].

Cerebriform connective tissue nevi (CCTN). Individuals with PS who develop large plantar CCTNs should receive regular dermatologic care and attention to manage malodor (a potential complication of difficulty with cleanliness of the deepening of the sulci in late adolescence) and other concerns, such as pressure ulcerations. Large plantar CCTNs can also contribute to problems with shoe fit and often warrant pedorthic intervention as mentioned above. Surgical removal of a CCTN has been successfully accomplished in at least two individuals.

Overgrowth of lipomatous tissue / lipoatrophy. Management of the overgrowth of adipose tissue is challenging because the areas of adipose overgrowth are not encapsulated and discrete (in contrast to lipomas) and, therefore, can be difficult to resect and commonly regrow after surgical debulking. The authors generally recommend open surgical approaches over liposuction because the highly vascularized lipomatous overgrowth in some individuals can result in difficult-to-control hemorrhaging and/or chronically weeping lymphatics.

Deep vein thrombosis (DVT) and pulmonary embolism (PE). The authors recommend emergent evaluation of individuals who develop symptoms of DVT (e.g., palpable subcutaneous rope-like mass, swelling, erythema, pain, and distal venous congestion) or PE (e.g., shortness of breath, chest pain, and cough which may include hemoptysis). Because individuals with PE can be asymptomatic, it is recommended that an individual with a DVT be evaluated for PE regardless of symptoms.

- **Evaluation for DVTs.** In the absence of cardiopulmonary compromise, consider the D-dimer assay and/or ultrasonographic evaluation.
- **Evaluation of PE.** High-resolution chest CT (so called spiral CT) with contrast is recommended. Ventilation-perfusion nuclear medicine scanning may be appropriate in some individuals.

Treatment of DVT and PE should follow recommended anticoagulation guidelines for these disorders. The authors recommend hematologic evaluation and consultation for consideration of anticoagulant prophylaxis for individuals undergoing surgery or other procedures that may predispose to DVT/PE.

Tumors. It is impractical to screen for tumors with imaging in individuals with PS because the tumors are so heterogeneous. Instead, a primary care clinician should evaluate the individuals regularly (every 6-12 months) and elicit signs and symptoms of malignancy (e.g., pain, unexpected growths, signs of obstruction or compression). If these are elicited, an imaging evaluation of that organ system should be undertaken.

Bullous pulmonary disease. Pulmonary evaluation is recommended for individuals with bullous pulmonary disease, and resection of large bullous lesions may be indicated in some individuals. Bullous disease in the context of scoliosis can pose significant and complex challenges for appropriate management.

Psychometric and learning evaluation. Developmental evaluation for consideration of intervention or special education for those individuals with developmental delays is indicated.

Psychosocial issues. Psychosocial counseling is certainly warranted in most instances. Although PS is exceedingly rare, a robust support group infrastructure exists and many families find this very helpful (see Resources).

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.

Because of the predisposition to a range of tumors (most of which are benign) individuals with PS should be monitored by their primary care provider with regular evaluations including a directed medical history and examination; periodic imaging is not indicated.

Agents/Circumstances to Avoid

Medications that increase the risk of DVT or are procoagulant should be avoided. Medications that increase growth (e.g., androgenic steroids or 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.

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

Search ClinicalTrials.gov in the US and www.ClinicalTrialsRegister.eu in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Proteus syndrome (PS) is not inherited.

- There are no confirmed occurrences of vertical transmission or sib recurrence.
- The molecular data show that all affected persons are mosaic for the same *AKT1* pathogenic variant (c.49G>A), suggesting that the variant occurred post fertilization in one cell of the multicellular embryo.

Risk to Family Members

Parents of a proband. No parent of a child with bona fide PS has been demonstrated to have any significant, distinctive manifestations of the disorder, nor would such a finding be expected, given the somatic mutational mechanism of the disease.

Sibs of a proband. Given the somatic mutational mechanism of PS, 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 are very limited. There are no instances of vertical transmission of PS.

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

Related Genetic Counseling Issues

Considerations in families with an apparent *de novo* mosaic pathogenic variant. This is a relatively new area for clinical genetics as there are only a small (although growing) number of disorders known to be caused by this genetic mechanism.

Counseling for recurrence risks in PS should emphasize that, while no pregnancy is at zero risk, all evidence suggests that the risk of recurrence for this disorder is not increased, compared to the general population.

Family planning

- 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.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing

Ultrasound examination. Atypical PS (i.e., the uncommon prenatal form with hemimegencephaly) may be detectable using prenatal ultrasound, but no examples are known to the authors. 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).

Molecular genetic testing. As PS is typically not prenatal in onset, and is not inherited, prenatal testing is not indicated.

One theoretic (and speculative) exception may be consideration of prenatal testing for the *AKT1* p.Glu17Lys pathogenic variant in a simplex occurrence of prenatal-onset hemimegencephaly.

Preimplantation genetic diagnosis (PGD). The authors recognize no potential role for PGD in PS.

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.

- **Proteus Family Network UK**
  United Kingdom
  Phone: 01785 661263
  Email: info@proteus.org.uk
  www.proteus-uk.org
- **Proteus Foundation**
  4915 Dry Stone Drive
  Colorado Springs CO 80918
  Phone: 719-660-1346
  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 genes 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.
- *PIK3CA* pathogenic variants have been demonstrated in a number of clinically diverse overgrowth syndromes including CLOVE syndrome [Kurek et al 2012] and a phenotype termed fibroadipose overgrowth [Lindhurst et al 2012]. See *PIK3CA*-Related Segmental Overgrowth [Keppler-Noreuil et al 2014].

Gene structure. *AKT1* extends over approximately 26 kb and includes 14 exons. The mRNA is approximately 3 kb, the reference cDNA is 3,008 bp (NM_005163.2), and the open reading frame is 1,443 bp. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. Only the c.49G>A (p.Glu17Lys) *AKT1* variant has been associated with PS.

Of note, this variant has also been identified as being somatically acquired in a number of tumors (see COSMIC). A synonymous variant in *AKT1* has been associated with schizophrenia [Tan et al 2008].

Normal gene product. The gene encodes a protein of 480 amino acids (NP_005154.2).

Abnormal gene product. It has been shown that the p.Glu17Lys pathogenic variant 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].

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Chapter Notes

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- 10 January 2019 (lgb) Revision: Category C criteria corrected (added bullous pulmonary degeneration)
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- 9 August 2012 (me) Review posted live
- 19 April 2012 (lgb) Original submission

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