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Mosaic Disorders of the PI3K/PTEN/AKT/TSC/mTORC1 signaling pathway

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Abstract

Mosaicism is the presence of two or more genetically distinct cell lineages originating from a single zygote. The skin frequently marks mosaic conditions through migration patterns of a population of mutant cells during embryogenesis. Somatic mutations in genes of the PI3K/PTEN/AKT/TSC/mTORC1 signaling pathway can result in segmental overgrowth, hamartomas, and malignant tumors, given the crucial role of this axis in cell growth. Mosaicism for activating mutations in *AKT1* and *PIK3CA* is responsible for Proteus syndrome and PIK3CA-Related Overgrowth Spectrum, respectively. These frequently exemplify Happle's patterns of cutaneous mosaicism. Postzygotic mutations in *PTEN* and *TSC1/TSC2* result in mosaic forms of the PTEN Hamartoma Tumor Syndrome and tuberous sclerosis complex, which may present as disseminated or segmental disease. Distinct features observed in these mosaic conditions may be attributed to differences in embryological timing or tissue type harboring the mutant cells. Deep sequencing methods of affected tissue is often necessary to diagnosis these disorders. Oral mTORC1 inhibitors, such as sirolimus and everolimus, are useful for treating tuberous sclerosis complex, and drugs targeting mTORC1 or other points along this signaling pathway are in clinical trials to treat several of these disorders.

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Introduction

Mosaicism may occur as a somatic mutation occurring during embryogenesis, resulting in an organism is composed of two (or more) genetically distinct cell lineages.[1] The resulting phenotype depends on the numbers and organization of abnormal cells in relation to normal cells and how the mutation affects cellular function.[2, 3] When the mutation affects cell signaling pathways regulating cell growth, apoptosis, or migration, dramatic regional alterations in the appearance of the skin can occur sometimes with regional overgrowth or tumor susceptibility. Dermatologists are frequent observers of these mosaic conditions and play important roles in diagnosis and management.

Somatic mutations in any of the genes in the PI3K/PTEN/AKT/TSC/mTORC1 signaling pathway (Figure 1) may result in a spectrum of abnormal growth ranging from an isolated small skin lesion with minimal or no overgrowth to extensive skin involvement with striking extremity enlargement and tumor susceptibility.[4–7] Proteus syndrome, caused by mutations in *AKT1*, and the *PIK3CA*-Related Overgrowth Spectrum (PROS) may be considered archetypal mosaic disorders, given the patchy distribution of disease features.[8, 9] Tuberous sclerosis complex (TSC), caused by mutations in either *TSC1* or *TSC2*, and *PTEN* Hamartoma Tumor Syndrome (PHTS) are most frequently associated with germline mutations, but mosaic forms also appear as isolated (simplex or sporadic) occurrences.[10–12] This review will primarily focus on these entities, chosen for their shared abnormalities in a signaling pathway and analogous or overlapping phenotypes.

PI3K/PTEN/AKT/TSC/mTORC1 signaling pathway and overgrowth

Cell growth is mediated by extracellular cues and may occur via increasing cell mass or cell division or by suppression of apoptosis. Mechanistic Target Of Rapamycin Complex 1 (mTORC1) is a central regulator of cell growth[13] disrupted in many human disorders of cell proliferation including cancers.[4, 5, 13–15] Under normal conditions, mTORC1 is sensitive to inputs from diverse cellular and environmental cues (Figure 1) including the phosphoinositide-3-kinase (PI3K) pathway. In short, growth factors stimulate PI3K, which then converts phosphatidylinositol 4,5-bisphosphate (PIP2) to phosphatidylinositol (3,4,5)-trisphosphate (PIP3) and permits activation of AKT. PTEN dephosphorylates PIP3 to PIP2, thereby exerting inhibitory control on AKT. [16]AKT phosphorylates several proteins including the TSC1-TSC2 complex, and thus alleviates negative control on mTOR to promote cell growth (Figure 1).

PTEN, TSC1, and TSC2 are tumor suppressors. For each of these genes, a germline mutation causes a loss of function allele, leading to a syndrome with susceptibility to multiple tumors. Tumorigenesis involves inactivation of the second allele, typically via a second-hit somatic mutation in the wild-type allele.[6, 16] Loss of function of *PTEN* results in

increased levels of PIP3 and alleviates inhibitory control on AKT to cause tumor formation in PHTS.[17] Biallelic mutations in *TSC1* or *TSC2* result in increased Ras homolog enriched in brain (Rheb)-GTP, which activates signaling through mTORC1, causing tumor formation in TSC.[18] While the PHTS and TSC are typically caused by germline mutations, both can have mosaic presentations, often with mild disease or later onset than inherited disease.[11, 19–23]

PIK3CA, a gene encoding the catalytic subunit of PI3K, and *AKT1* are oncogenes and thus a gain of function, or activating mutation in only one copy of the allele is the mechanism of disease.[24, 25] Strongly activating mutations in these genes may only be seen in patients through mosaicism.[26, 27] Point mutations activating *PIK3CA* have been documented in a variety of mosaic disorders captured under the umbrella term PROS.[9, 27] The mosaic presence of an activating mutation in *AKT1* results in Proteus syndrome.[26, 28]

Phenotype of disorders of the PI3K/PTEN/AKT/TSC/mTORC1 signaling pathway

Mosaic-only oncogenes

It is widely regarded that strongly activating germline mutations in *AKT1* and *PIK3CA* are lethal, with few reported exceptions.[9, 26, 29] Mutations in these genes result in distinctive segmental, or asymmetric overgrowth syndromes that can involve the bone, muscle, adipose tissue, skin and/or nerves and may be relatively stable (*PIK3CA*) or progressive (*AKT1* or *PIK3CA*) in course.[309, 26, 31, 32] The severity of the overgrowth may range from a slightly enlarged digit to a gigantic limb.[33, 34] Hamartomas, or benign, focal overgrowths resembling their tissue of origin, may also be present.[35] The epidermal nevus and vascular malformation in these disorders (Figure 2A,B) are examples of the Blaschkoid and checkerboard patterns of cutaneous mosaicism, respectively.[36]

Somatic activation in *AKT1* has been linked to Proteus syndrome, an extraordinarily rare disorder (incidence is less than 1 case per 10 million) that is characterized by sporadic occurrence, asymmetric distribution of lesions and progressive course.[26, 37] Frequent dermatologic lesions include cerebriform connective tissue nevi, lipomas, linear keratinocytic epidermal nevus, and lymphovascular malformations.[8]

PROS represents a broad constellation of somatic disorders caused by activating mutations in *PIK3CA* including CLOVES syndrome (Congenital Lipomatous Overgrowth, Vascular malformations, linear keratinocytic Epidermal nevi and Skeletal/spinal anomalies), Fibroadipose hyperplasia or Overgrowth (FAO), Hemihyperplasia Multiple Lipomatosis (HHML), certain megalencephaly syndromes, isolated macrodactyly, isolated lymphatic malformations, seborrheic keratoses, and benign lichenoid keratoses.[30, 38, 39] The phenotype of this spectrum ranges from isolated disease, such as macrodactyly, megalencephaly, or vascular malformations, to syndromes defined by tissue overgrowth, vascular malformations and epidermal nevi.[9, 30, 40, 41] As several individuals with Klippel-Trenaunay syndrome (KTS), which bears clinical semblance to PROS, have been recently attributed to *PIK3CA* mutations, KTS may be under the PROS umbrella.[42]

Germline or mosaic tumor suppressor genes

PHTS represents a spectrum of diseases caused by mutations in the PTEN tumor suppressor gene, including Cowden syndrome and Bannayan-Riley-Ruvalcaba Syndrome (BRRS).[43] Cowden syndrome is an autosomal-dominant condition characterized by skin hamartomas and mixed benign and malignant tumors of the thyroid, breast and endometrium. [44] Characteristic mucocutaneous lesions include trichilemmomas, acral keratoses and oral papillomatosis and are usually present by the third decade.[10, 44] Malignancy risk is greatest for breast cancer (approximately 85%), and is increased for thyroid cancer, endometrial cancer and colon cancer and melanoma.[43]

BRRS is usually congenital in onset and cutaneous manifestations include pigmented macules of the glans penis[45], although formal diagnostic criteria have not yet been defined.[43] Given the clinical overlap and known allelism of BRRS and Cowden syndrome, some assert that they are one condition with distinct manifestations in childhood and adulthood, respectively.[46]

For conditions with autosomal-dominant inheritance, three categories of mosaicism exist (Figure 3).[3] Disseminated mosaicism is perhaps the most common; the phenotype is usually clinically similar to germline disease with multiple lesions and/or tumors.[1, 36, 47] Segmental mosaicism may be categorized based on the genetic background of the organism. Type 1 segmental mosaicism describes a localized postzygotic heterozygous mutation in an organism with two otherwise normal alleles, resulting in expected disease manifestations restricted to a discrete region. Type 2 segmental mosaicism describes an organism with a localized postzygotic mutation in *trans* (i.e., on the otherwise normal allele) to a mutant allele that was inherited from a heterozygous parent, resulting in biallelic mutations in some cell lines. If the heterozygous mutant state causes disease, as in TSC or PHTS, then type 2 segmental mosaicism results in a clinical phenotype with a more severe segment of disease in a patient with otherwise typical disease distribution.[1, 36, 47–49]

Mosaicism has been genetically confirmed in several cases among the 10–40% of patients with *de novo* mutations in *PTEN*.[10] The majority of reports describe disseminated mosaicism, resulting in an anatomically diffuse distribution of cutaneous hamartomas and mixed internal lesions that are clinically difficult to distinguish from inherited or *de novo*, non-mosaic Cowden syndrome disease.[19, 20, 50] Interestingly, there have also been isolated occurrences of patients with germline *PTEN* mutations that harbor loss of *PTEN* heterozygosity in lesions not characteristic of Cowden syndrome or BRRS.[22, 51] Because of its distinct clinical picture, type 2 segmental mosaicism for *PTEN* was termed ‘SOLAMEN syndrome’ to reflect the presence of features consistent with a germline *PTEN* mutation in addition to Segmental Overgrowth, Lipomatosis, Arteriovenous Malformations and Epidermal Nevi.[2246] Similarly, an overgrowth of fat, blood vessels and fibrous tissue (termed the PTEN hamartoma of soft tissue) has been described in individuals with Cowden syndrome and BRRS[52], although type 2 segmental mosaicism of the *PTEN* gene has not been molecularly confirmed in these lesions.

TSC is a neurocutaneous syndrome inherited in an autosomal-dominant pattern characterized by hamartomas in multiple organ systems, including the brain, kidneys, lungs

and skin.[53, 54] Hypomelanotic macules, angiofibromas, shagreen patches, ungual fibromas and fibrous cephalic plaques are among the most frequent and specific cutaneous findings.[55–57] Oral findings include oral fibromas and dental enamel pits.[57, 58] Non-invasive, visceral hamartomas can be harmful due to hemorrhage risk or impingement on adjacent structures.[12] A subset of TSC patients have no mutation identified using conventional analysis, and many of these patients are mosaic.[11] A postzygotic mutation in *TSC1* or *TSC2* before neural crest cell differentiation may explain disseminated TSC-related skin lesions, including bilateral angiofibromas (Figure 2C), ungual fibromas and hypomelanotic macules.[11, 59–62] Unilateral facial angiofibromas are suspected to represent type 1 segmental mosaicism (Figure 2D,E).[63]

Comparing phenotypes

Although these disorders are distinctive, there is overlap in the phenotypes associated with mutations of *PIK3CA, PTEN*, *TSC1, TSC2* and *AKT1*, which may be expected given their common pathway and mosaic pathogenesis. Disorders of this axis may be broadly characterized by frequency of one or more of the following features: segmental overgrowth, hamartomas or malignant tumors (Table 1). As all four conditions are characterized by hamartomas, Table 2 contrasts the specific types of hamartomas observed in these conditions.

Proteus syndrome and PROS may be difficult to clinically distinguish; however, stable course and/or lack of cerebriform connective tissue nevus may point towards a PROS diagnosis.[9] Type 2 segmental Cowden syndrome may also resemble Proteus syndrome or PROS, but can be identified by presence of orofacial papules and/or hamartomas of the thyroid, breast and endometrium.[22]

Proposed mechanisms of phenotype divergence

Timing of mutations

Variation in the timing of post-zygotic mutations may cause phenotypic variability, conferring a spectrum of disease burden. In TSC and PHTS, individuals with an early postzygotic mutation often have similar disease features and distribution of disease as those with a germline mutation.[19, 20, 50, 59] More specifically, postzygotic mutations occurring before or after cell differentiation events may explain certain disease presentations. For example, a *TSC2* mutation occurring during neuroectodermal development may explain the presence of tubers in TSC, but the absence of subependymal nodules[64], while a mutation in neural crest cells after migration from the neural tube may account for complete absence of neuroanatomical brain involvement in these patients.[65] A *PIK3CA* mutation that occurs prior to germ layer differentiation may manifest as multisystem disease in PROS with cortical abnormalities (ectodermal origin) and capillary malformations (mesodermal origin).[30] In contrast, a localized postzygotic mutation will produce disease manifestations restricted to tissue type and/or a segment of the body, as demonstrated in a case of Proteus syndrome with only bilateral cerebriform connective tissue nevus and lower extremity varicose veins.[66]

Tissue specificity

In addition to timing of mutation, tissue type in which the mosaic mutation resides appears to influence the clinical presentation; for instance, an activating *AKT1* mutation in keratinocytes is responsible for epidermal nevus formation, yet the same mutation in fibroblasts produces an entirely different clinical entity (i.e., the cerebriform connective tissue nevus).[67] In some cases, mutation in a cell restricted to a certain germ layer may additionally affect tissues from a separate layer through cell signaling. Indeed, fibroblast-like cells in TSC-related hamartomas have been shown to release paracrine factors that affect the overlying epidermis.[68]

Diagnosis of mosaicism

Clinical diagnosis alone is often difficult for these conditions, given substantial overlap of characteristic features. While traditional genetic analysis of mosaic patients can be equally difficult, sampling the affected tissue, rather than blood, using deep sequencing methods appears to have greater diagnostic accuracy.[11, 19, 22, 66, 67, 69, 70] For instance, studies suggest that up to 15% of patients with TSC may be mosaic; however, conventional sequencing methods may fail to detect low levels of the mutant allele in the blood.[11, 59–61, 71] Next generation sequencing techniques that analyze angiofibroma samples for genetic mutations are promising to close the diagnostic gap for patients with no mutation identified from blood samples.[11, 69] A similar approach has been utilized by harvesting epidermal nevi, vascular malformations or overgrown muscle samples to allow molecular diagnosis in patients with Proteus syndrome and PROS.[26, 30, 40, 67, 70, 72] Mutational analysis of resected dysplastic cerebellar tissue in Cowden syndrome has also been employed for mosaic diagnosis.[19] As all of the conditions discussed here present with at least some pathogenic skin findings, sequencing of DNA isolated from cutaneous tissue samples may be the least invasive, yet effective, way of arriving at molecular diagnosis for these patients.

While genetic testing may be helpful to guide patient management, caution should be taken when interpreting results. Thus far, the frequency of mutant cells in affected or normal tissue does not accurately correlate with disease burden in disorders of this pathway.[9, 20, 67, 69]

Counseling for prognosis and management

The presence of seemingly benign skin findings or highly limited disease involvement may have greater clinical importance than is apparent. This example has been recently demonstrated in TSC, where patients with mild clinically apparent disease in fact harbored serious internal manifestations that caused morbidity and sometimes, mortality.[12, 73] Thus, lifetime surveillance for brain, pulmonary and renal hamartomas is necessary for all patients with TSC, including those with mosaic mutations.[74] While rare, malignant transformation of benign tumors in TSC has reported.[75] In patients with PHTS, characteristic cutaneous hamartomas may signal the presence of, or impending risk for, internal malignancies. Thus, patients with mosaic and germline PTEN mutations should be routinely monitored for breast, endometrial and thyroid cancers according to current guidelines, as even patients with a low frequency of mutant cells may have increased cancer risk.[19, 44]

There have been reports of nephroblastomatosis (a premalignant lesion) and Wilms tumor in several patients with PROS and hemihyperplasia.[9, 27, 40, 76] Based upon literature citing a 3.3–6% risk of tumorigenesis for embryonal tumors in isolated hemihyperplasia, there may be a similar risk for patients with PROS.[76–78] Thus, preliminary recommendations for surveillance have been proposed, including serial ultrasounds of the abdomen, but further data is needed to confirm prevalence of tumorigenesis.[30] While the risk of malignancy in Proteus syndrome and PROS is unknown, the risk of thrombosis and subsequent pulmonary embolism is substantial for patients with Proteus syndrome and PROS. This appears to be most threatening when patients undergo surgery and surgeons need to be aware of this risk. Patient education regarding symptoms suggestive of a thromboembolism is also important.[9, 37]

In addition to disease surveillance, reproductive counseling for patients with mosaic disorders warrants special mention. For patients with mosaicism for *TSC1, TSC2* or *PTEN*, mosaic cells may be present in the gonads. Thus, a patient with limited mosaic disease involvement could give birth to a severely affected (non-mosaic) child. [1] The chance that an offspring of a mosaic individual would be affected is difficult to estimate and such patients should be referred for genetic counseling. On the other hand, gonadal mosaicism for a mutation in either *AKT1* or *PIK3CA* is not likely to result in a viable fetus.[26, 79]

SUMMARY

The mosaic disorders of the PI3K/PTEN/AKT/TSC/mTORC1 signaling pathway share a common axis, but distinct mutations in this pathway are associated with highly variable clinical presentations that are recognizable. These clinical presentations should be genetically confirmed because each condition has unique implications for disease management. This common pathway may provide insight into treatment. For instance, oral mTORC1 inhibitors have shown to reduce the disease burden in TSC[74, 80], have shown promise for vascular malformations and PHTS[74, 81, 82], and are currently being investigated for PROS. In vitro studies suggest that direct inhibition of *AKT1* or *PIK3CA* may be useful for Proteus syndrome (clinical trial in progress) and PROS.[28, 83]

Understanding how mutations in these genes intersect with one signaling pathway explains the similarity among their clinical presentations and provides rationale for practical therapeutic approaches. Further, recognizing how mosaic involvement leads to variations in patterning explains the patchy and often asymmetric distribution of cutaneous and systemic involvement. The study of mosaic conditions along this pathway may also provide insights into the role of the PI3K/PTEN/AKT/TSC/mTORC1 pathway in skin biology, thereby improving understanding of common dermatological problems.

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Abbreviations and Acronyms

PROS	PIK3CA-Related Overgrowth Spectrum
TSC	tuberous sclerosis complex
PHTS	PTEN Hamartoma Tumor Syndrome
mTORC1	mechanistic Target Of Rapamycin Complex 1
PI3K	phosphoinositide-3-kinase
PIP2	phosphatidylinositol (4,5)-bisphosphate
PIP3	phosphatidylinositol (3,4,5)-trisphosphate
Rheb	Ras homolog enriched in brain
FAO	Fibroadipose hyperplasia or Overgrowth
HHML	Hemihyperplasia Multiple Lipomatosis
KTS	Klippel-Trenaunay syndrome
BRRS	Bannayan-Riley-Ruvalcaba Syndrome

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Key Points

- Mosaicism may be considered in sporadic cases; there should be a negative history in ancestral generations or siblings, but offspring may be affected through gonadal mosaicism.
- A patchy distribution of cutaneous features and tissue overgrowth or disseminated disease that is mild should raise suspicion for mosaicism.
- Next-generation sequencing, or other methods for detecting low frequency alleles, of affected tissue is frequently necessary to identify the genetic basis of mosaic conditions.
- Drugs that target proteins along the PI3K/PTEN/AKT/TSC/mTORC1 signaling pathway have shown promise in the treatment of these disorders.

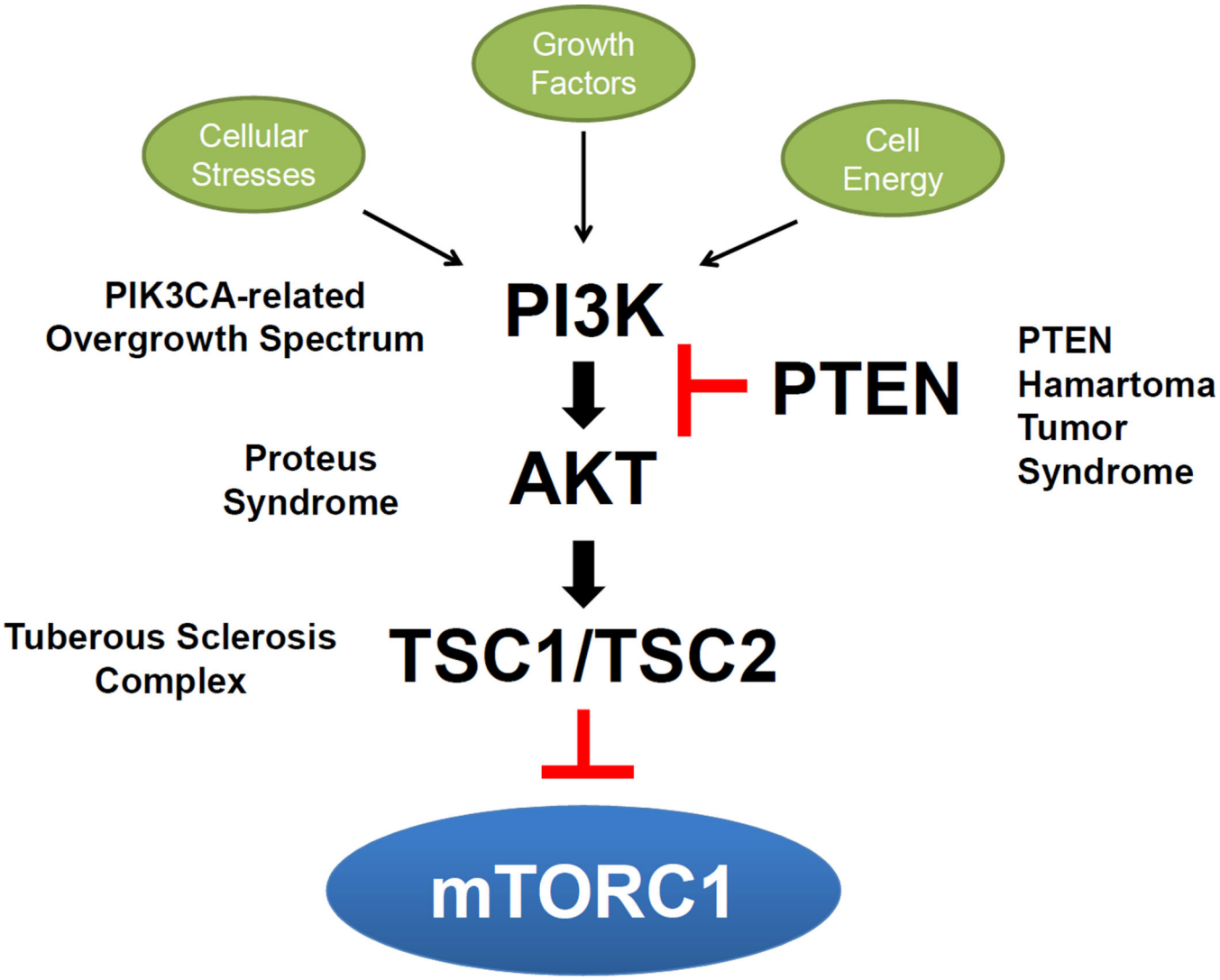

Figure 1.
Disorders of the mTORC1 signaling pathway.

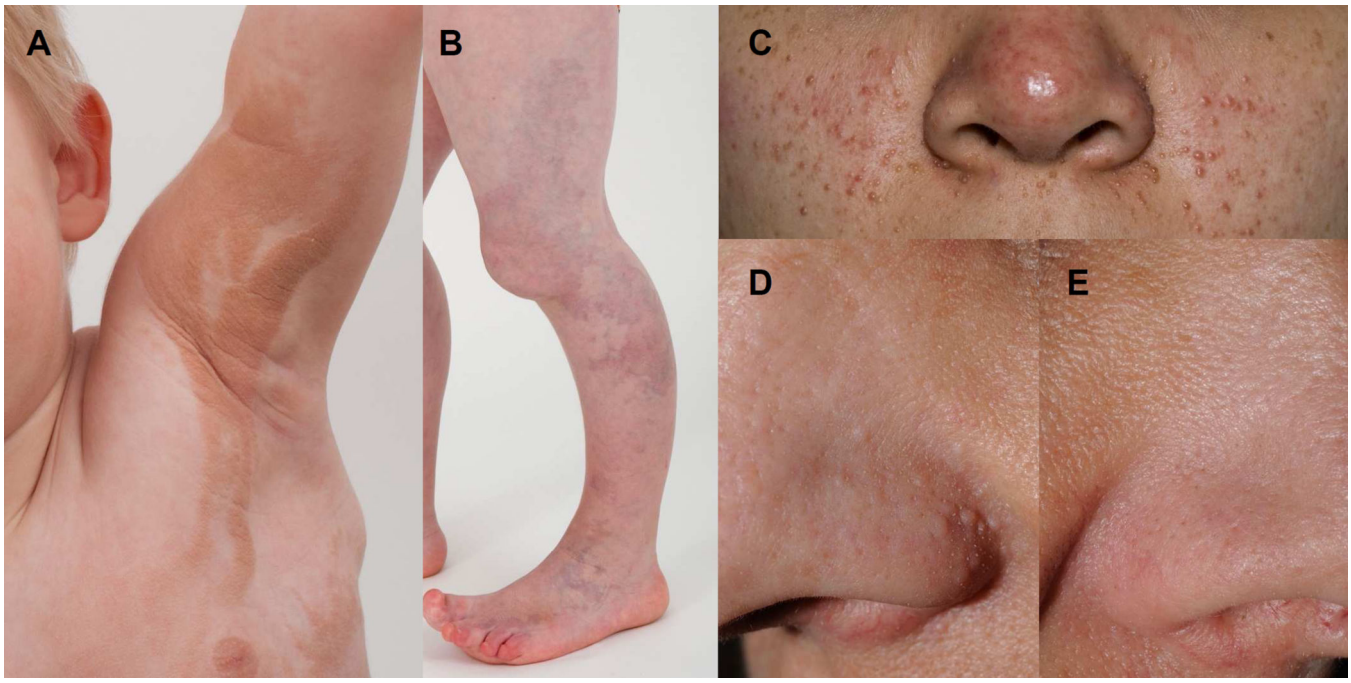

Figure 2.

Patterns of cutaneous mosaicism. Blaschkoid pattern of an epidermal nevus (A) and checkerboard pattern of a capillary malformation (B) in children with Proteus syndrome. Disseminated (C) and type 1 segmental mosaicism (D,E) in women with tuberous sclerosis complex. Angiofibromas are observed in the left nasal groove (D) but absent from the right in the same individual (E). Written informed consent for patients included in this figure was obtained according to NIH protocols 00-H-0051, 95-H-0186, and/or 82-H-0032 (C-E).

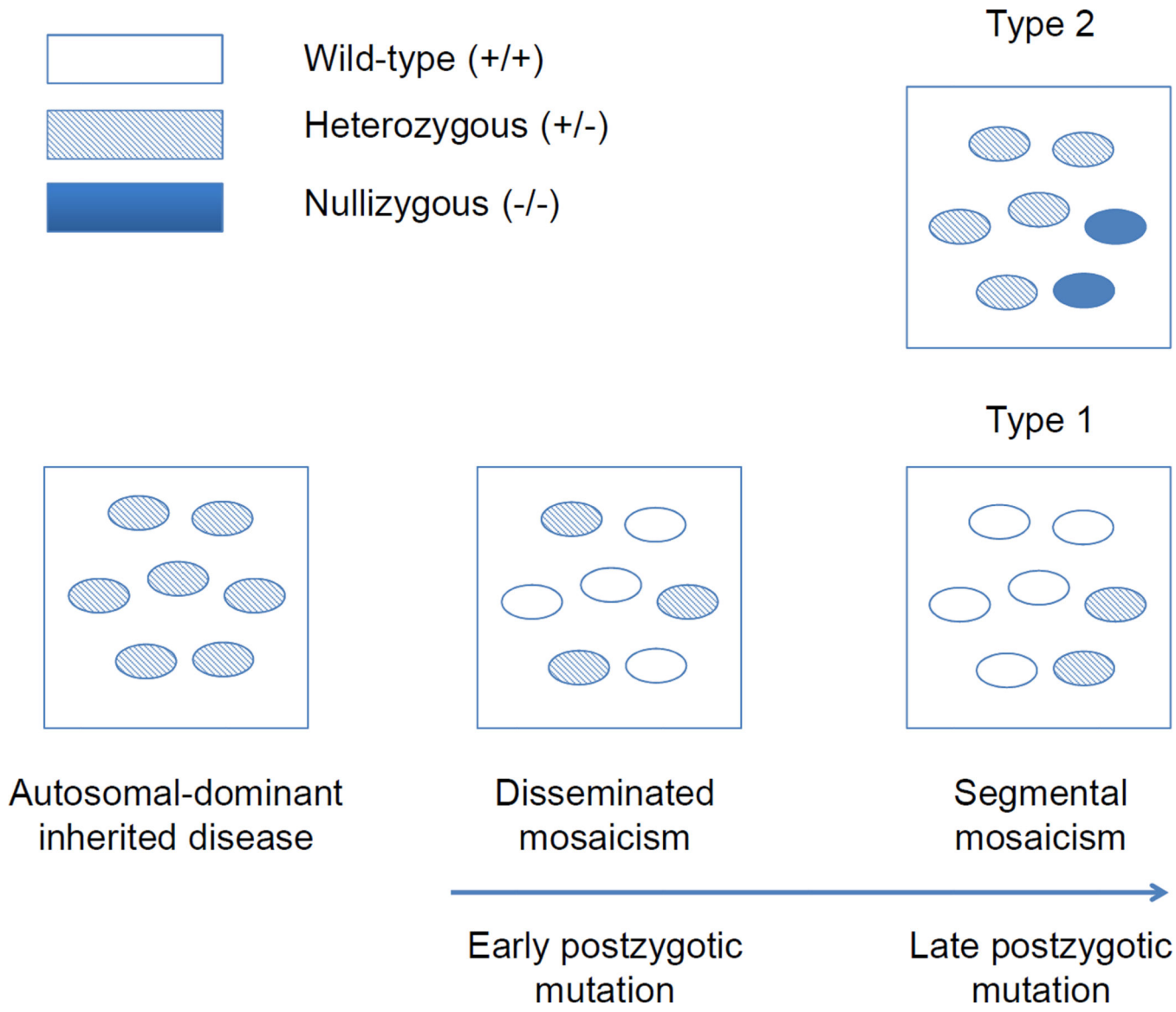

Figure 3.

Types of mosaicism in autosomal dominant conditions. Each square represents an individual and ovals represent cells. In disseminated mosaicism, a postzygotic mutation occurs relatively early in development so that mutant cells are scattered amongst normal cells throughout the body. In type 1 segmental mosaicism, a postzygotic mutation occurs that is limited to certain body regions. In type 2 segmental mosaicism, the individual inherits only one functional copy of the gene and late in embryogenesis, a postzygotic mutation occurs, resulting in a region that is nullizygous with accentuated disease.

Table 1

Types of abnormal growth observed with mosaic mutations of the PI3K/PTEN/AKT/TSC/mTORC1 signaling pathway.

	PIK3CA	***PTEN***	***AKT1***	***TSC1/TSC2***
	PROS	**PHTS**	**Proteus Syndrome**	**Tuberous Sclerosis Complex**
Segmental Overgrowth	***	*	***	*
Hamartomas	***	***	***	***
Malignant Tumors	*	***	*	*

*** common;

* uncommon;

PHTS, PTEN Hamartoma Tumor Syndrome; PROS, *PIK3CA*-Related Overgrowth Spectrum.

Table 2

Mucocutaneous hamartomas of mosaic disorders of the PI3K/PTEN/AKT/TSC/mTORC1 signaling pathway.

	PIK3CA	***PTEN***	***AKT1***	***TSC1/TSC2***
	PROS	**PHTS**	**Proteus Syndrome**	**Tuberous Sclerosis Complex**
Facial papules		***		***
Epidermal nevus	***	*	***	*
Connective tissue nevus	*	*	***	***
Cutaneous vascular malformation	***	*	***	*
Oral papules		***		***

*** common;

* uncommon;

PHTS, PTEN Hamartoma Tumor Syndrome; PROS, *PIK3CA*-Related Overgrowth Spectrum.