Clinics in Dermatology (2016) **34**, 183–204

Clinics in Dermatology

Cutaneous and ocular manifestations of neurocutaneous syndromes

Karen A. Chernoff, MD, Julie V. Schaffer, MD*

Ronald O. Perelman Department of Dermatology, New York University School of Medicine, New York, NY 10016, USA

Abstract Neurocutaneous syndromes are a heterogeneous group of congenital and hereditary disorders with manifestations in the skin and the nervous system, usually together with ocular features that represent diagnostic clues and potential sources of morbidity. Dermatologists and ophthalmologists often need to work together in identifying and managing patients with these conditions; herein, we focus on classic and under-recognized neurocutaneous syndromes. We begin with autosomal dominant genodermatoses characterized by hamartomas and tumors in the skin, eyes, and central nervous system: neurofibromatosis type 1, tuberous sclerosis complex, and PTEN hamartoma-tumor syndrome. This is followed by a discussion of two mosaic disorders, Sturge-Weber syndrome and neurocutaneous melanocytosis. In addition to providing an update on clinical presentations and evaluation of patients with these conditions, we review recent insights into their pathogenesis, drawing attention to relationships among the diseases on a molecular level and implications regarding treatment. We also highlight the major features of other neurocutaneous syndromes that have ocular findings plus pigmentary, vascular, hyperkeratotic, adnexal, connective tissue, photosensitive, and inflammatory manifestations in the skin.

Overview of neurocutaneous syndromes

Neurocutaneous syndromes represent a heterogeneous group of congenital and hereditary disorders with manifestations in both the skin and the nervous system, usually together with characteristic ocular features. These diseases are traditionally known as "phakomatoses" (Greek *phakos*: lentil, birthmark), a term coined by the Dutch ophthalmologist Jan van der Hoeve in 1923 to emphasize the patchy nature of the clinical findings in neurofibromatosis and tuberous sclerosis. Van der Hoeve later expanded this group to include von Hippel–Lindau and Sturge-Weber syndromes, and ataxia-telangiectasia was added in 1941. A variety of other conditions have subsequently been classified as phakomatoses, with some authors limiting the category to disorders characterized by neurocutaneous hamartomas and/or tumors.

The constellation of features in some neurocutaneous syndromes reflects the fact that affected tissues share an embryonic origin in the neural crest.[1] The neural crest represents a transient population of embryonic cells that arise from ectoderm and migrate outward from the dorsal region of the neural tube. Upon reaching their final destinations, neural crest cells differentiate into a wide variety of cells and structures. Neural crest–derived cell populations include melanocytes of the skin and eye, Schwann cells of peripheral nerves, chromaffin cells of the adrenal medulla, glomus cells, and the leptomeninges.[2] In patients with neurofibromatosis (see later), these cell types are implicated in pigmented skin

* Corresponding author. Tel.: +1 212 263 5245.
E-mail address: Julie.schaffer@nyumc.org (J.V. Schaffer).

http://dx.doi.org/10.1016/j.clindermatol.2015.11.003
0738-081X/

lesions, Lisch nodules, neurofibromas, pheochromocytomas, and glomus tumors, respectively. Enteric ganglion cells and craniofacial mesoderm, including the membranous bones of the face and cranium, also originate from the neural crest.[3,4] This explains the Hirschsprung disease and facial dysmorphism as well as leukoderma, heterochromia irides, and deafness (due to the importance of melanocytes in the stria vascularis of the cochlea) observed in Waardenburg syndrome, a classic neurocristopathy. Of note, considering the frequency of ocular findings in neurocutaneous syndromes, structures of the eye with neural crest lineage range from the sclera and the stroma of the cornea, iris, and choroid to the ciliary and extraocular muscles.

Although dermatologists are generally familiar with the skin findings of neurocutaneous syndromes, they must also be aware of ocular manifestations that represent diagnostic clues and potential sources of morbidity. Dermatologists and ophthalmologists often need to work together in identifying and managing patients with these disorders, which commonly requires the input of neurologists, geneticists, and other subspecialists. This paper focuses on several important neurocutaneous syndromes, including classic phakomatoses with prominent cutaneous and ocular manifestations (neurofibromatosis type 1, tuberous sclerosis complex, and Sturge-Weber syndrome) as well as PTEN hamartoma-tumor syndrome and neurocutaneous melanocytosis. In addition to providing an update on clinical manifestations and evaluation of these conditions, we review recent insights into their pathogenesis, drawing attention to relationships between the disorders on a molecular level and implications regarding treatment. Tables 1 through 5 highlight the major features of other neurocutaneous syndromes that have ocular findings plus pigmentary, vascular, hyperkeratotic, adnexal, connective tissue, photosensitive, and inflammatory manifestations in the skin.

Neurofibromatosis type 1

Neurofibromatosis type 1 (NF1; von Recklinghausen disease) is the most common neurocutaneous disorder, affecting roughly 1 in 3000 individuals worldwide. It is inherited in an autosomal dominant manner, with up to 50% of patients harboring a new spontaneous mutation in the *NF1* gene and therefore having unaffected parents.[5,6] Although penetrance approaches 100%, expressivity is highly variable in individuals with a constitutional (germline) *NF1* mutation. In addition, mosaicism for a *NF1* mutation can lead to segmental forms of NF1 with pigmentary and/or neural manifestations.

The *NF1* gene encodes neurofibromin, a GTPase-activating protein (GAP) that functions as a negative regulator of Ras signaling (Figure 1).[7,8] Ras requires GTP binding for full activity in stimulating the mitogen-activated protein kinase (MAPK) pathway, which promotes cell proliferation. By accelerating the hydrolysis of GTP to GDP, neurofibromin decreases Ras activity and thereby functions as a tumor suppressor protein. In patients with NF1, loss-of-function mutations in the *NF1* gene lead to inappropriate activation of the Ras-MAPK pathway and a predisposition for tumorigenesis. Neurofibromin is expressed in migrating neural crest cells during embryogenesis, and its particular importance to this lineage explains the Schwann cell- and melanocyte-derived oculocutaneous manifestations of NF1.[9] Similar to other autosomal dominant tumor predisposition syndromes caused by a defective tumor suppressor gene, a somatic "second hit" mutation that inactivates the remaining *NF1* allele can be found within skin lesions, such as the Schwann cells of neurofibromas and the melanocytes of café-au-lait spots (CALS).[10]

Cutaneous and ocular findings account for five of the seven diagnostic criteria for NF1 developed by the National Institutes of Health.[11] A clinical diagnosis requires two of the following: (1) ≥ 6 CALS (size >5 mm prepuberty, >15 mm postpuberty); (2) ≥ 2 neurofibromas or ≥ 1 plexiform neurofibroma; (3) freckling in the axillae or groin; (4) optic glioma; (5) ≥ 2 Lisch nodules; (6) sphenoid dysplasia or cortical thinning of long bones; and (7) a first-degree relative with NF1. Approximately 70% of all patients with NF1 and 45% of those without an affected relative can be diagnosed by 1 year of age using the National Institutes of Health criteria.[12]

Commercially available testing can identify a pathogenic *NF1* mutation in $\geq 95\%$ of nonfounder patients who meet the National Institutes of Health criteria. This allows NF1 to be diagnosed in young children who do not (yet) fulfill two clinical criteria.[13] It can also point to possible alternative diagnoses (eg, Legius syndrome) in patients who meet criteria for NF1 but do not have an identifiable *NF1* mutation (see later).[14]

Cutaneous manifestations of NF1

Skin lesions with melanocytic origin

Pigmented lesions are of great aid in establishing the diagnosis of NF1 due to their early age of onset and almost ubiquitous occurrence, with the occasional exception of patients with predominantly spinal neurofibromatosis.[15] CALS represent the most common clinical finding in NF1, with $\geq 99\%$ of patients developing ≥ 6 of these lesions by 1 year of age.[12] In patients with NF1, CALS are typically well demarcated with smooth borders and homogenous pigmentation (Figure 2A).[16] Their color ranges from tan to dark brown, and fading often occurs during adulthood.[17] When biopsied, CALS in patients with NF1 show an increased concentration of melanin within the epidermis. Some studies have noted a higher melanocyte density and frequency of giant melanosomes compared with sporadic CALS.[18,19]

In the general pediatric population, approximately 25% to 35% of children have at least one CALS, but $<1\%$ of children have ≥ 4 of these lesions.[20] The morphology of CALS is

Table 1 Selected neurocutaneous disorders with pigmentary manifestations

Disorder	Major cutaneous findings	Potential neurologic findings	Potential ocular findings
Hyperpigmented lesions			
Neurofibromatosis type 1 *	• See text	• See text	• See text
Neurofibromatosis type 2	• Schwannomas—plaques, often with hyperpigmentation and hypertrichosis, or nodules (50%-70% of patients) • Neurofibromas (uncommon) • CALS (typically ≤ 5; ~50% of patients)	• Bilateral vestibular schwannomas—hearing loss, tinnitus • Meningiomas, spinal cord ependymomas • Neuropathy	• Cataracts (60%-80% of patients) • Epiretinal membranes, retinal hamartomas • Strabismus, amblyopia
LEOPARD syndrome *	• Lentigines, café-noir spots	• Intellectual disability • Hearing deficit	• Hypertelorism, epicanthal folds, ptosis
Noonan syndrome *	• CALS, melanocytic nevi • Keratosis pilaris ± atrophicans • Lymphedema • Curly hair	• Intellectual disability • Hypotonia	• Hypertelorism, epicanthal folds, ptosis • Strabismus, refractive errors • Blue-green irides
Cardiofaciocutaneous syndrome *	• Melanocytic nevi > CALS • Keratosis pilaris ± atrophicans • Focal PPK • Infantile hemangiomas • Curly hair, sparse eyebrows	• Intellectual disability • Hypotonia, seizures	• Hypertelorism, epicanthal folds, ptosis • Strabismus, refractive errors, nystagmus
Mismatch repair cancer syndrome	• CALS, intertriginous freckling • Hypopigmented macules • Neurofibromas	• CNS gliomas	• Lisch nodules (uncommon) • Optic glioma (uncommon)
PTEN hamartoma-tumor syndrome	• See text	• See text	• See text
Hypo- and/or hyperpigmentation			
Tuberous sclerosis	• See text	• See text	• See text
"Pigmentary mosaicism": hypomelanosis of Ito, linear and whorled nevoid hypermelanosis	• Streaks/swirls of hypo- or hyperpigmentation along Blaschko lines	• Intellectual disability Seizures	• Variable
Incontinentia pigmenti	• Streaks/swirls of reticulate gray-brown hyperpigmentation (stage 3) • Linear erythema with vesicles (stage 1) or verrucous plaques (stage 2) • Hypopigmented, hairless bands favoring calves (stage 4)	• Intellectual disability • Seizures, spasticity	• Retinal vascular abnormalities • Strabismus, cataracts, optic atrophy
Dyskeratosis congenita	• Reticulated hyperpigmentation or poikiloderma • Nail dystrophy > PPK, palmoplantar hyperhidrosis	• Intellectual disability (uncommon) • Cerebellar ataxia (Hoyeraal-Hreidarsson variant)	• Lacrimal duct atresia, entropion, trichiasis, keratoconjunctivitis, retinal abnormalities, cataracts (uncommon)
Xeroderma pigmentosum †	• Solar lentigines • Guttate hypopigmentation, poikiloderma • Photosensitivity • Nonmelanoma skin cancer > melanoma	• Hyporeflexia, seizures • Hearing deficit	• Conjunctivitis, keratitis, corneal neovascularization and scarring, xerophthalmia, blepharitis, ectropion
Chédiak-Higashi syndrome	• Diffuse pigmentary dilution • Hyperpigmentation and guttate hypopigmentation in sun-exposed areas • Silvery hair	• Sensory and motor neuropathies • Progressive ataxia • Intellectual decline	• Lightly pigmented eyes • Photophobia, nystagmus, strabismus

(continued on next page)

Table 1 (*continued*)

Disorder	Major cutaneous findings	Potential neurologic findings	Potential ocular findings
Waardenburg syndrome	• Depigmented patches on forehead, mid extremities; islands of sparing and CALS • White forelock	• Hearing deficit	• Heterochromia irides • Dystopia canthorum • Synophrys
Dermal melanocytosis			
Nevus of Ota	• Speckled/mottled blue-gray facial patches, usually unilateral	• Leptomeningeal melanocytosis (uncommon)	• Blue-gray pigmentation of the sclera > iris, choroid; rarely melanoma • Iris mammillations • Glaucoma (uncommon)
Hurler syndrome, GM1 gangliosidosis (GM1-G)	• Extensive dermal melanocytosis (eg, anterior + posterior trunk) • Angiokeratoma corporis diffusum (GM1-G)	• Neurodevelopmental deterioration	• Corneal clouding, glaucoma, retinal degeneration (Hurler) • Cherry-red macular spot (GM1-G)

CALS, café-au-lait spots; *CNS,* central nervous system; *PPK,* palmoplantar keratoderma.

* RASopathies; similar pigmentary findings may be seen in Costello syndrome (see Table 4).

† Other photosensitive neurocutaneous disorders can present with pigmented lesions, such as Cockayne and Bloom syndromes (see Table 5).

another important consideration. In a recent series of 110 children (median age 3 years) with multiple CALS but no other features of NF1, 77% (34/44) of those with ≥ 6 "typical" lesions were eventually diagnosed with NF1, compared with 15% (2/15) of those with ≥ 6 "atypical" lesions that had smudgy, irregular borders and nonhomogeneous pigmentation.[16] Irregular CALS with a "paint-splashed" border, especially when multiple lesions are grouped in the same region or on one side of the body, may reflect "pigmentary mosaicism" due to a nonspecific chromosomal abnormality within lesional skin.

Intertriginous "freckling" (Crowe sign) presents as numerous 1- to 4-mm brown macules that represent smaller versions of CALS, actually more akin to lentigines than ephelides. Although these lesions favor the axilla (Figure 2B) and groin, they often occur in other sites such as the neck, lower face, and trunk. Approximately 90% of NF1 patients develop intertriginous freckling by 4 to 6 years of age.[12]

Although previously considered to be pathognomonic for NF1, intertriginous freckling can also occur in piebaldism and Legius, LEOPARD, and mismatch repair cancer syndromes (see Table 1).[21–25] Patients with these conditions often have CALS as well, and thus can meet criteria for NF1. *Legius syndrome* (previously known as NF1-like syndrome) is an autosomal disorder caused by mutations in the *SPRED1* gene, which encodes a protein that interacts with neurofibromin and inhibits MAPK signaling.[26] Features include multiple CALS (~80% of patients), intertriginous freckling (~50% of patients), lipomas, vascular anomalies, macrocephaly, and learning disabilities; however, Lisch nodules, optic gliomas, and neurofibromas are not seen.[23]

Skin lesions with neural origin

Cutaneous (dermal) neurofibromas typically begin to develop around puberty but may appear as early as 4 to 5 years of age. Less than half of children with NF1 have clinically evident neurofibromas by 10 years of age,[12] with plexiform (see later) rather than cutaneous lesions predominating in this age group. In contrast, cutaneous neurofibromas are present in ~85% of adults with NF1.

Classic cutaneous neurofibromas are dome-shaped or pedunculated, soft to rubbery papulonodules that are skin colored, pinkish, or hyperpigmented (Figure 2B, C). They have a highly characteristic "buttonhole" sign of invagination when gentle pressure is applied; however, some neurofibromas, especially early lesions, are barely elevated or even macular. These under-recognized variants include *blue-red macules* (with prominent blood vessels in the upper dermis; see Figure 2C), which favor the trunk and are seen in ~8% of adults with NF1, and *pseudoatrophic macules* (with reduced dermal collagen).[27] *Subcutaneous neurofibromas* represent a deeper subtype that tends to be firmer and less sharply marginated than purely dermal lesions. In addition to Schwann cells, both cutaneous and subcutaneous neurofibromas are composed of perineural cells, fibroblasts, and mast cells. Of note, recent studies suggest that mast cells have a key role in promoting neurofibroma formation.[28]

Plexiform neurofibromas affect ~25% of individuals with NF1[29] and are typically congenital in origin due to an early postzygotic "second-hit" *NF1* mutation. They usually become clinically apparent by 3 to 5 years of age, with the exception of smaller deep or internal lesions. Plexiform neurofibromas may extend along a nerve, forming firm nodules or masses that are tender and described as having a "bag of worms" consistency upon palpation; they can also diffusely infiltrate the skin and underlying tissues. Hyperpigmentation, hypertrichosis, and thickening of the overlying skin are common findings (Figure 2D), which may lead to misdiagnosis as a congenital melanocytic nevus.[30]

Table 2 Selected neurocutaneous disorders with vascular manifestations

Disorder	Major cutaneous findings	Potential neurologic findings	Potential ocular findings
Von Hippel–Lindau disease	• None	• Hemangioblastomas of brain and spinal cord	• Hemangioblastomas of the retina
Ataxia telangiectasia	• Telangiectasias (eg, on ears, cheeks, upper trunk) • CALS, hypopigmented macules • Progeric facies, premature grey hair • Papulosquamous facial rash, granulomas	• Ataxia, dysarthria, bradykinesia (in first few years of life)	• Conjunctival telangiectasias (medial and lateral; mean onset age 4-6 years)
Sturge-Weber syndrome	• See text	• See text	• See text
Microcephaly-capillary malformation syndrome	• Multiple capillary malformations—small and widespread	• Progressive microcephaly	• Hypertelorism, ptosis • Optic atrophy
Familial cerebral cavernous malformations	• Hyperkeratotic capillary-venous malformations (~10% of patients)	• Cerebral capillary malformations • Headaches, seizures, cerebral hemorrhage	• Retinal vascular malformations (~5% of patients)
Wyburn-Mason (Bonnet-Dechaume-Blanc) syndrome	• Facial AVM	• Brain AVM • Seizures, hemiparesis	• Orbital AVM
PTEN hamartoma-tumor syndrome	• See text	• See text	• See text
PHACE syndrome	• Segmental infantile hemangioma, usually on the face	• Cerebrovascular abnormalities • Posterior fossa malformations	• Retinal vascular anomalies • Optic nerve hypoplasia
Prolidase deficiency	• Acral telangiectasias • Leg ulcers	• Intellectual disability	• Hypertelorism, ptosis, exophthalmos
Fabry disease *	• Angiokeratoma corporis diffusum (favoring bathing trunk area) • Hypohidrosis	• Acral pain and paresthesias • Cerebrovascular disease (eg, stroke)	• Corneal (whorled) and lenticular opacities • Tortuous vessels of eyelid, conjunctiva, and retina
Homocysinuria	• Malar flush, livedo reticularis, thrombosis, atrophic scars • Diffuse pigmentary dilution of skin and hair	• Intellectual disability	• Lens subluxations (downward)

AVM, arteriovenous malformation; *CALS,* café-au-lait spots; *PHACE,* posterior fossa malformations, hemangioma, arterial anomalies, cardiac defects, and eye anomalies.

* Other lysosomal storage diseases (eg, fucosidosis, [galacto]sialidosis) can present with angiokeratoma corporis diffusum together with ocular findings (eg, corneal opacities, cherry-red macular spots, conjunctival telangiectasias) and neurodevelopmental deterioration.

Large, bulky plexiform neurofibromas can cause soft tissue and bony hypertrophy that result in disfigurement. Lesions involving the orbit (see later), airway, or spine tend to be especially problematic.[31] Roughly 10% of plexiform neurofibromas undergo transformation into a malignant peripheral nerve sheath tumor (neurofibrosarcoma). This has a peak incidence in young adults and is often heralded by persistent pain, a new neurologic deficit, increased firmness, or rapid growth of a previously stable plexiform neurofibroma.[18]

Vascular lesions of the skin

Vascular anomalies that have recently been recognized as manifestations of NF1 include *nevus anemicus* and *glomus tumors*.[32–35] In a large prospective study, a nevus anemicus was identified in 51% (77/151) of patients with NF1 (59% [58/98] of children and 36% [19/53] of adults), compared with only 2% (6/302) of age- and sex-matched controls.[35] The nevus anemicus was most often on the chest in both groups. Interestingly, one third (2/6) of the sporadic lesions but none of the 77 NF1-associated lesions were accompanied by a port-wine stain. Because the NF1-associated nevus anemicus is often apparent in the first 2 years of life, its use as an early clinical marker has been proposed.[34,35]

In a recent series of glomus tumors identified in a pathology database, 29% (6/21) of the patients had NF1.[36] NF1-associated glomus tumors tend to be multiple and affect the fingers more than toes. Like their sporadic counterparts, they typically present with paroxysmal pain and sensitivity to cold, often in an ill-defined area of reddish discoloration and swelling.[32] Biallelic inactivation of the *NF1* gene within these lesions has been described in NF1 patients.[33]

Table 3 Selected neurocutaneous disorders with hyperkeratotic or adnexal manifestations

Disorder	Major cutaneous findings	Potential neurologic findings	Potential ocular findings
Ichthyosis			
X-linked recessive ichthyosis	• Widespread brown adherent scales, favoring the neck	• Intellectual disability (uncommon; associated with larger deletions)	• Corneal opacities
Sjögren-Larsson syndrome	• Widespread hyperkeratosis ± scaling, favoring flexures and the lower abdomen; pruritus; PPK	• Spasticity, diparesis/ tetraparesis, seizures, intellectual disability	• Perifoveal glistening white dots, crystalline macular dystrophy • Photophobia, decreased visual acuity
Neutral lipid storage disease	• Widespread scaling with variable erythema	• Intellectual disability • Hearing deficit	• Cataracts
Multiple sulfatase deficiency	• Similar to X-linked recessive ichthyosis	• Neurodevelopmental abnormalities • Hearing deficit	• Cataracts
Refsum disease	• Scaling on extremities > trunk	• Neuropathy, ataxia • Hearing deficit	• Retinitis pigmentosa • Cataracts
Arthrogryposis-renal dysfunction-cholestasis (ARC) syndrome	• Widespread scaling that spares skin folds	• Neurodevelopmental abnormalities Hearing deficit	• Corneal opacities
Colobomas, heart defects, ichthyosiform dermatosis, mental retardation, and ear anomalies (CHIME) syndrome *	• Migratory ichthyosiform eruption	• Intellectual disability • Seizures	• Colobomas (retinal, choroidal) • Hypertelorism, epicanthal folds
Rhizomelic chondrodysplasia punctata	• Ichthyosis then follicular atrophoderma	• Neurodevelopmental abnormalities	• Cataracts
Cerebral dysgenesis, neuropathy, ichthyosis and keratoderma (CEDNIK) syndrome	• Widespread scaling with variable erythema; PPK	• Microcephaly, abnormal corpus callosum, intellectual disability • Neuropathy • Hearing deficit	• Hypertelorism, downward-slanting palpebral fissures • Optic atrophy
Erythrokeratoderma, palmoplantar keratoderma/pitting, and epidermal nevi			
Keratitis-ichthyosis-deafness (KID) syndrome	• Keratotic plaques, follicular or diffuse hyperkeratosis; grainy PPK; cheilitis • Follicular occlusion triad, cysts, adnexal neoplasms, SCC	• Hearing deficit	• Keratitis
Ichthyosis follicularis, atrichia, and photophobia (IFAP) syndrome	• Follicular keratoses, psoriasiform plaques • Congenital atrichia	• Intellectual disability, seizures	• Keratitis
Richner-Hanhart syndrome (tyrosinemia type II)	• Focal PPK	• Progressive intellectual disability	• Dendritic keratitis, corneal ulcers
Sebaceous nevi (SN), epidermal nevi (EN; subset of nonepidermolytic lesions)	• Waxy yellowish (SN) and tan-to-brown hyperkeratotic or papillomatous (EN) plaques along Blaschko's lines • Adnexal neoplasms (SN)	• Neurodevelopmental abnormalities	• Coloboma, choristoma, lipodermoids
Nevoid BCC syndrome	• Early-onset BCCs • Palmoplantar pits	• Macrocephaly, calcification of falx cerebri • Medulloblastoma	• Hypertelorism • Subconjunctival epithelial cysts • Strabismus • Cataracts, colobomas
Hypotrichosis			
Trichothiodystrophy	• Short, fragile hair • Variable ichthyosis, photosensitivity, and nail dystrophy	• Intellectual disability	• Cataracts

Table 3 (*continued*)

Disorder	Major cutaneous findings	Potential neurologic findings	Potential ocular findings
Menkes disease	• Sparse, lightly pigmented, kinky hair (pili torti) • Lax skin with diffuse pigmentary dilution	• Neurodevelopmental deterioration, seizures	• Poor visual acuity/ myopia, strabismus • Blue irides

PPK, palmoplantar keratoderma; *BCC,* basal cell carcinomas; *SCC,* squamous cell carcinomas.
* Similar findings are seen in the type Iq congenital disorder of glycosylation.

Other skin findings

As many as 15% to 30% of children with NF1 are diagnosed with one or more *juvenile xanthogranulomas* during the first 2 to 3 years of life.[34,37] The lesions are often multiple and favor the face, scalp, and groin. A "triple association" among NF1, juvenile xanthogranulomas, and juvenile myelomonocytic leukemia has

Table 4 Selected neurocutaneous disorders affecting the connective tissue

Disorder	Major cutaneous findings	Potential neurologic findings	Potential ocular findings
Encephalocraniocutaneous lipomatosis	• Lipomas and fibromas favoring eyelids and scalp, with overlying alopecia (nevus psiloliparus)	• Intracranial lipomas, vascular abnormalities, and cysts	• Choristomas
Oculocerebrocutaneous (Delleman) syndrome	• "Skin tags" with skeletal muscle • ACC over ears	• Agenesis of corpus callosum, giant tectum-absent vermis	• Microphthalmia, orbital cysts
Focal dermal hypoplasia	• Dermal atrophy, fat "herniation," telangiectasias, and dyspigmentation along Blaschko lines; scalp ACC • Periorificial papillomas	• Intellectual disability • Myelomeningocele	• Colobomas, aniridia, microphthalmia • Ectopia lentis • Poor visual acuity
Microphthalmia with linear skin defects syndrome (MIDAS syndrome)	• Stellate ACC on face and neck	• Intellectual disability, seizures • Hypoplasia of corpus callosum, microcephaly	• Microphthalmia • Sclerocornea • Cataracts • Retinal abnormalities
Pseudoxanthoma elasticum	• Yellowish, cobblestone, sagging plaques on neck and in other flexures	• Cerebrovascular disease (eg, stroke)	• Angioid streaks, mottling of retinal pigment epithelium Choroidal neovascularization & hemorrhage
AR cutis laxa type II, including De Barsy syndrome (DBS)	• Loose, sagging skin; favors hands/feet in IIB	• Neurodevelopmental abnormalities • Pachygyria (IIA) • Hypoplasia of corpus callosum, dystonia (IIB/DBS)	• Downward-slanting palpebral fissures • Strabismus, high myopia (IIA) • Corneal opacities, cataracts (IIB/DBS)
Costello syndrome	• Lax acral skin • Acanthosis nigricans, periorificial papillomas • Nevi, lentigines • Curly hair, early androgenetic alopecia	• Intellectual disability • Seizures	• Hypertelorism, epicanthal folds, ptosis • Strabismus, refractive errors
Lipoid proteinosis	• Vesicles/erosions → "ice pick" scars • Waxy thickening of skin and oropharynx; verrucous plaques on elbows/knees	• Temporal lobe calcifications • Neuropsychiatric abnormalities, seizures	• Beaded papules along eyelid margins • Prominent corneal nerves; corneal ulcers (uncommon)
Hunter syndrome	• Pebbly papules in scapular region	• Neurodevelopmental abnormalities	• Optic atrophy, retinopathy
Cerebrotendinous xanthomatosis	• Tuberous and tendinous xanthomas	• Neurodevelopmental and psychiatric abnormalities, ataxia, dystonia • Neuropathy	• Cataracts • Optic disc pallor, retinal vessel sclerosis

ACC, aplasia cutis congenita; *AR,* autosomal recessive; *MIDAS,* microphthalmia, dermal aplasia and sclerocornea.

Table 5 Selected neurocutaneous disorders presenting with photosensitivity and/or inflammatory skin lesions

Disorder	Major cutaneous findings	Potential neurologic findings	Potential ocular findings
Cockayne syndrome *	• Photosensitivity, solar lentigines (less than in XP), atrophic skin • Cyanotic acral edema	• Neurodevelopmental abnormalities • Microcephaly • Hearing deficit	• Sunken eyes • Pigmentary retinal degeneration, optic atrophy • Cataracts • Microphthalmia, iris hypoplasia
Bloom syndrome	• Photosensitivity, malar erythema and telangiectasias • CALS	• Microcephaly, intellectual disability (mild)	• Conjunctival telangiectasias • Retinal drusen
Rothmund-Thomson syndrome †	• Facial erythema and edema → poikiloderma on face, dorsal hands, buttocks • Photosensitivity (variable) • Acral keratoses, ulcers and SCC	• Intellectual disability (mild; uncommon)	• Cataracts • Corneal abnormalities • Sparse eyelashes
Aicardi-Goutières syndrome	• Acral chilblain lupus	• Neurodevelopmental deterioration • Microcephaly, white matter changes	• Abnormal eye movements
Hartnup disease	• Photosensitive pellagra-like dermatitis	• Intermittent ataxia • Psychiatric disturbances	• Intermittent nystagmus
Biotinidase and holocarboxylase synthetase deficiencies	• Periorificial erythema and erosions • Alopecia	• Neurodevelopmental abnormalities, hypotonia, seizures • Hearing deficit	• Conjunctivitis, blepharitis • Optic atrophy
Phenylketonuria	• Diffuse pigmentary dilution of skin and hair • Eczematous dermatitis • Sclerodermatous changes of proximal extremities	• Neurodevelopmental deterioration	• Blue irides • Cataracts
Cryopyrin-associated periodic syndromes	• Urticarial papules and plaques (may be cold induced)	• Headache, aseptic meningitis • Hearing deficit	• Conjunctivitis, uveitis, optic disc edema
Blau syndrome	• Granulomatous dermatitis	• Cranial neuropathies • Seizures • Cerebral arteritis	• Uveitis • Cataracts, glaucoma
Psoriasiform dermatitis, microcephaly and developmental delay	• Psoriasiform dermatitis	• Neurodevelopmental abnormalities • Microcephaly	• Cataracts

CALS, café-au-lait spots; *SCC,* squamous cell carcinomas; *XP,* xeroderma pigmentosum.

* Photosensitivity is also a finding in XP (see Table 1).

† Poikiloderma with neutropenia, Clericuzi type, has similar features.

been described; however, the magnitude of additional risk of juvenile myelomonocytic leukemia in young children with NF1 plus juvenile xanthogranulomas compared with the 200- to 500-fold increased risk of juvenile myelomonocytic leukemia associated with NF1 alone (incidence of 1/2000 to 1/5000) remains to be determined.

Pruritus is a common manifestation of NF1. It is usually generalized but occasionally related to a particular neurofibroma or other skin lesion. The increased density of mast cells within neurofibromas and CALS may play a pathogenic role in NF1-associated itch.[19]

Ocular manifestations of NF1

Ocular lesions with melanocytic or neural origin

Lisch nodules are the most common ocular finding in NF1 and represent a useful clinical marker. Among patients with NF1, the prevalence of these pigmented iris hamartomas increases from ~40% at age 5 years to ~70% at age 10 years to ~95% in adults.[12] They appear as small (<1-2 mm), dome-shaped, well-defined yellow-brown papules on the iris (Figure 3), especially its inferior portion, and are best

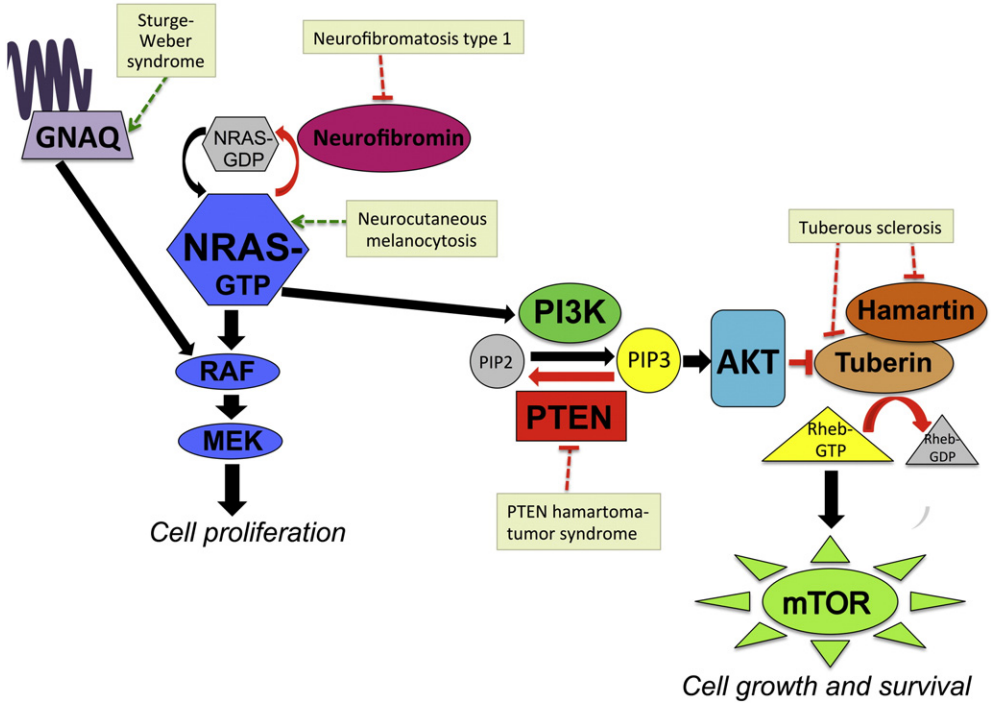

Fig. 1 Mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3 K)/AKT signaling pathway abnormalities in neurocutaneous syndromes. *GDP*, guanosine diphosphate; *GNAQ*, Q-class G protein α-subunit; *GTP*, guanosine triphosphate; *mTOR*, mammalian target of rapamycin; *PIP2/3*, phosphatidylinositol di/triphosphate.

visualized on slit-lamp examination.[38] In contrast, iris nevi are flat or slightly elevated, ill-defined, densely pigmented lesions. Because Lisch nodules are benign and do not impair vision, they are rarely biopsied. Reports of the histologic findings have described a mix of pigmented spindle-shaped cells containing melanosomes, fibroblast-like cells, and mast cells.[39] Whether the pigmented cells are of melanocytic or schwannian origin has been debated.[39,40]

Optic gliomas occur in 10% to 20% of patients with NF1[12,41,42] and usually develop before 7 years of age. Conversely, most optic gliomas occur in children with NF1.[43] These tumors represent benign, low-grade pilocytic astrocytomas that may affect the optic nerve, optic chiasm, optic tract, or hypothalamus. Although many patients remain asymptomatic, clinical manifestations can include decreased visual acuity, visual field defects, loss of color vision, proptosis, strabismus, and nystagmus. Ophthalmologic examination may also show optic disc pallor and a relative afferent pupillary defect. Children with hypothalamic involvement can develop precocious puberty, which may initially present with accelerated linear growth,[44] and larger tumors occasionally lead to hydrocephalus and signs of increased intracranial pressure.

In children with NF1, recommended monitoring for optic gliomas includes annual evaluation by an ophthalmologist until at least 8 years of age and then possibly biennially up to age 18.[42] Ophthalmologic assessment should include visual acuity, color vision, visual fields, ocular motility, pupillary reflexes, slit-lamp examination, and funduscopy.[45] Magnetic resonance imaging (MRI) of the brain and orbit is indicated if signs or symptoms develop. Although there has been debate in the literature regarding routine imaging, screening with MRI in asymptomatic individuals has not been found to be of benefit[31,42,46]; however, imaging may be considered when it is not possible to perform a reliable eye examination.

When *plexiform neurofibromas* affect the eyelid or orbit, consequences can include proptosis, strabismus, amblyopia, congenital glaucoma, and skull deformities. *Sphenoid dysplasia*, a bony defect in the posterior orbital wall, is typically associated with an orbital plexiform neurofibroma. This characteristic osseous lesion is included in the diagnostic criteria for NF1 and classically presents with pulsating exophthalmos within the first year of life.[12]

Studies using near-infrared reflectance imaging with confocal scanning laser ophthalmoscopy have found patchy *choroidal nodules* in 80% to 100% of adults and ~70% of children with NF1,[47,48] compared with <10% of unaffected individuals. This has led to a proposal that choroidal abnormalities be added to the diagnostic criteria for NF1. Recent reports have also drawn attention to *retinal vasoproliferative tumors*, which can lead to loss of vision, in patients with NF1.[49]

Other manifestations of NF1

Neurodevelopmental manifestations of NF1 can include learning disabilities (30%-50% of patients), attention deficit and autism spectrum disorders, and sleep disturbances. Brain MRI shows characteristic "unidentified bright objects" in 50%

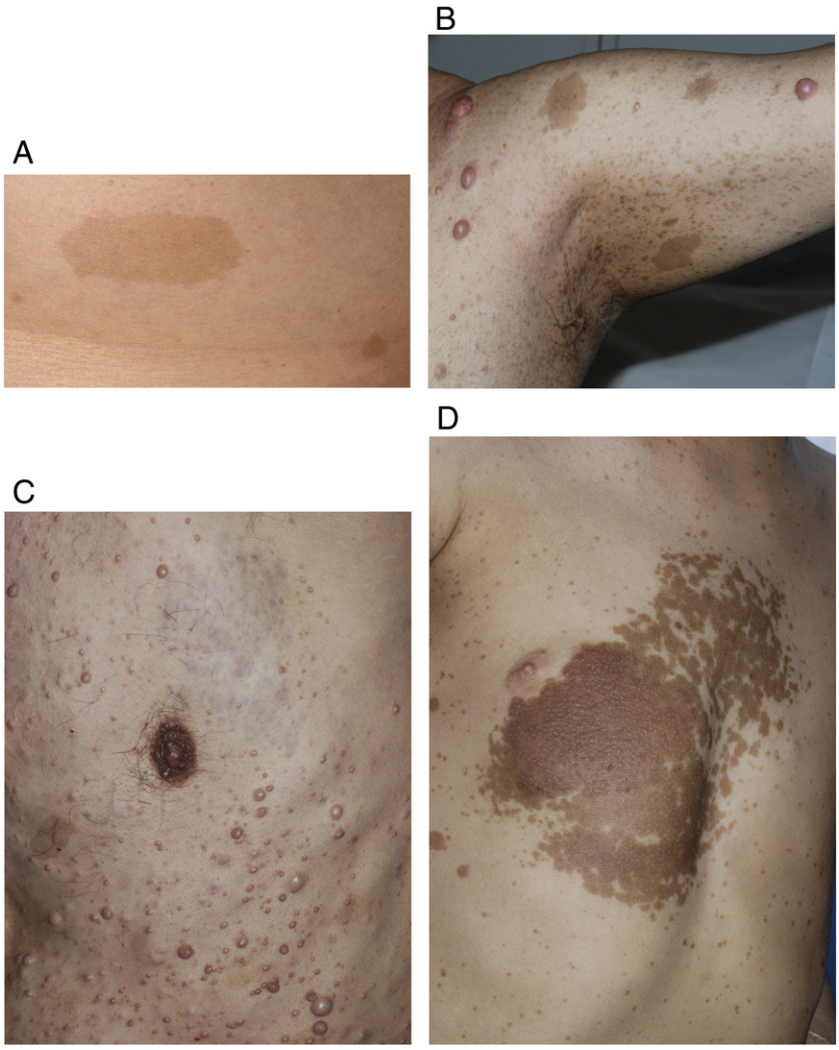

Fig. 2 Skin findings in patients with neurofibromatosis type 1. A, Café-au-lait spots with homogeneous pigmentation and smooth borders. B, Axillary "freckling," café-au-lait spots, and pink, dome-shaped neurofibromas. C, Larger blue-red macule as well as numerous small, dome-shaped neurofibromas. D, Plexiform neurofibroma presenting as a hyperpigmented plaque in a child. Such lesions may be misdiagnosed as congenital melanocytic nevi.

to 75% of patients, and central nervous system (CNS) tumors other than optic gliomas occasionally develop.[50] Macrocephaly is another common finding (30%-50% of patients).

Skeletal abnormalities associated with NF1 range from scoliosis (~10% of patients) to the more specific thinning of long bone cortex that can lead to pseudoarthrosis. NF1 patients have an increased risk of breast cancer (~fivefold elevation in women <50 years of age) and other tumors such as pheochromocytomas, gastrointestinal stromal tumors (GIST), and rhabomyosarcomas. NF1-associated cardiovascular abnormalities include essential hypertension (~30% of patients), renal artery or pulmonic stenosis, and cerebrovascular anomalies.[18]

Mosaic NF1

In segmental NF1 (formerly known as neurofibromatosis type 5), CALS, "freckling," and/or neurofibromas are found in a patchy distribution (eg, blocklike). This is a reflection of mosaicism due to a postzygotic mutation in the *NF1* gene. Affected individuals may meet criteria for NF1, but because only a limited portion of the body is affected, they have a substantially lower risk of extracutaneous manifestations; indeed, many patients with mosaic NF1 have only pigmentary lesions or only cutaneous neurofibromas. If the mutation involves the gonads in addition to the skin, however, there is a possibility of full-blown NF1 in the patient's offspring.

Advances in the management of NF1

Guidelines for the management of patients with NF1 have been published.[51,52] Recognition of the critical role of mast cells in neurofibroma tumorigenesis led to investigation of imatinib, an inhibitor of the c-Kit receptor on mast cells, as a treatment for plexiform neurofibromas. A promising initial

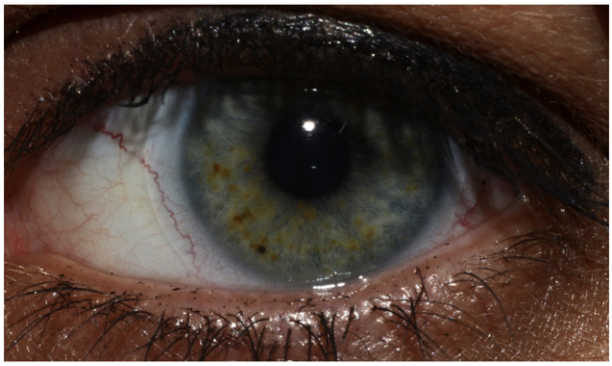

Fig. 3 Lisch nodules in a patient with neurofibromatosis type 1.

report described dramatic improvement in a life-threatening cervicofacial plexiform lesion after imatinib therapy[53]; however, only a modest benefit was seen in a recent phase 2 trial, with a 20% reduction in plexiform neurofibroma volume in 26% (6/23) of NF1 patients who received imatinib for at least 6 months.[54] Ongoing studies are evaluating targeted inhibition of other kinases, such as those in the MAPK pathway (eg, RAF, MEK) and vascular endothelial growth factor receptors, or mTOR inhibitors as potential therapies for tumors in NF1 patients.[55]

Table 6 2012 revised diagnostic criteria for tuberous sclerosis complex (TSC)

Major features
- Hypomelanotic macules (≥3, *at least 5 mm in diameter*)
- Angiofibromas (≥*3*) or fibrous *cephalic* plaque
- Ungual fibromas (≥*2*)
- Shagreen patch
- Multiple retinal hamartomas
- Cortical *dysplasias (including tubers and white matter radial migration lines)*
- Subependymal nodules
- Subependymal giant cell astrocytoma
- Cardiac rhabdomyoma
- Lymphangioleiomyomatosis (LAM)
- Angiomyolipomas (≥*2*)

Minor features
- "Confetti" skin lesions
- Dental enamel pits (≥*3*)
- *Intraoral* fibromas (≥*2*)
- Retinal achromic patch
- Multiple renal cysts
- Nonrenal hamartomas

Definite clinical diagnosis: 2 major features * –*or*– 1 major + 2 minor features

Possible clinical diagnosis: 1 major feature –*or*– 2 minor features

Definite genetic diagnosis: Identification of a pathogenic mutation in either *TSC1* or *TSC2* in DNA from normal tissue †

Adapted from Northrup and Krueger (2013).[67] Changes from the 1998 criteria are italicized.

* With the exception of LAM + angiomyolipomas.

† Approximately 10% to 25% of patients with TSC have no mutation identified by conventional genetic testing, so a normal result does not exclude TSC unless a known pathogenic mutation in an affected relative is excluded.

Tuberous sclerosis complex

Tuberous sclerosis complex (TSC) is another classic autosomal dominant neurocutaneous disorder, with a reported incidence of roughly 1 in 10,000 births[56,57]; however, considering the wide variability in expressivity, it is thought that the true incidence of TSC is actually higher due to the presence of undiagnosed mildly symptomatic individuals. Approximately two thirds of patients with TSC have a spontaneous new mutation.

TSC is caused by mutations in either of two genes, *TSC1* and *TSC2*. Familial cases are linked to each of the genes in roughly equal frequency, whereas *de novo* cases are four times more likely to be due to *TSC2* mutations. Individuals with *TSC2* mutations tend to have a more severe phenotype, with an increased likelihood of mental retardation.[58]

The *TSC1* and *TSC2* genes encode hamartin and tuberin proteins, respectively, which function together in a complex. Tuberin (like neurofibromin) has GAP activity. By accelerating the hydrolysis of GTP, tuberin "turns off" Rheb, a protein that stimulates the mammalian target of rapamycin (mTOR) pathway (see Figure 1). Loss-of-function mutations in TSC1 or TSC2, therefore, lead to inappropriate mTOR signaling, which results in increased cell growth and survival.[59–61] Patients with TSC can develop hamartomas in nearly any organ system, most often the skin, retina, brain, kidney, heart, and lung. Diagnostic criteria were created in 1992 and most recently revised in 2012 (Table 6). The importance of cutaneous, oral, and ocular findings as markers of TSC is underscored by the fact that 5 of the 11 major criteria and 4 of the 6 minor criteria involve the skin, mouth, or eyes. Dermatologists commonly have a role in diagnosing TSC, and skin lesions often represent the first signs of this condition.

Cutaneous, oral, and ocular manifestations of TSC

Hypopigmented lesions

Hypomelanotic macules represent the earliest and most prevalent (>90%) skin finding in patients with TSC.[62] Although often present at birth or within the first few months of life, these lesions may take longer and/or require examination with a Wood's lamp to become evident, especially in children with lightly pigmented skin. Small (<2 cm), polygonal or "thumbprint"-shaped hypopigmented macules are most common (Figure 4A), although their size

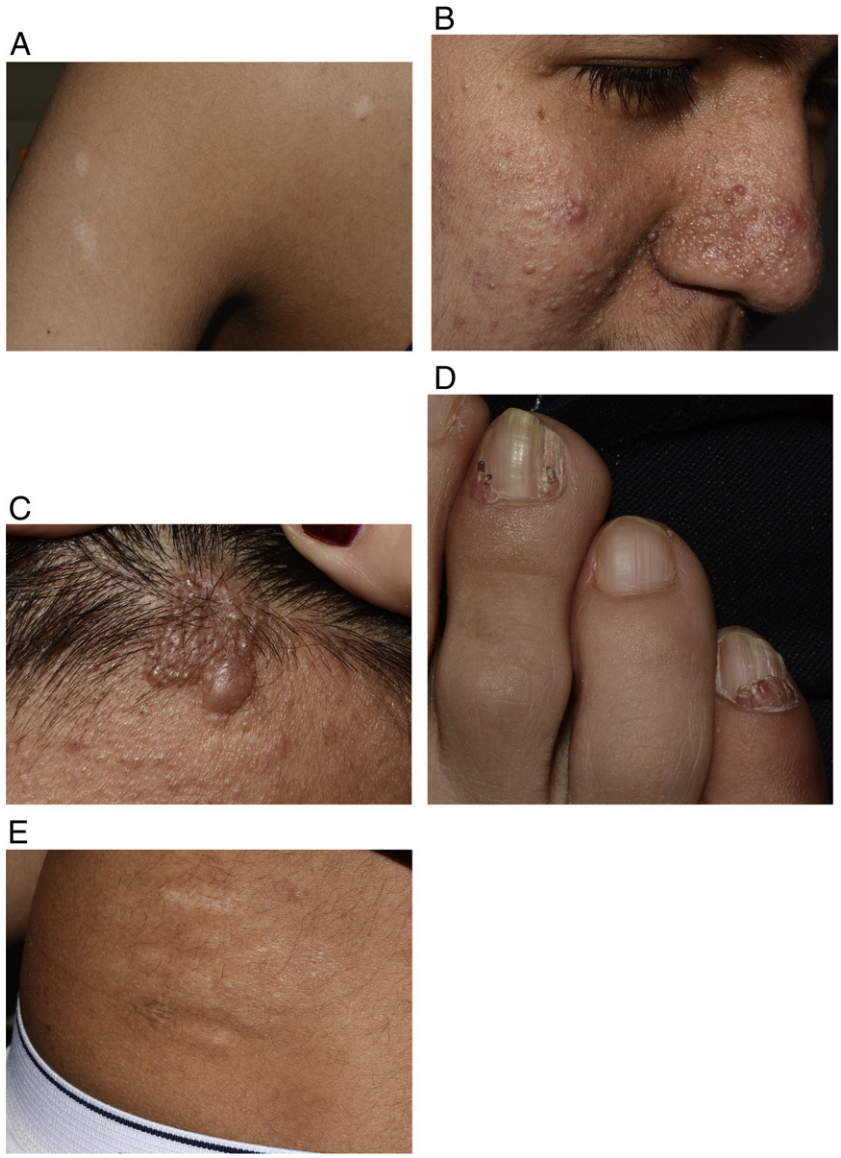

Fig. 4 Skin findings in patients with tuberous sclerosis. A, Multiple thumbprint-like hypomelanotic macules. B, Facial angiofibromas in an adolescent. C, Fibrous plaque on the forehead. D, Periungual fibromas on the toes. E, Shagreen patch with prominent follicular orifices.

can reach > 10 cm and the characteristic lance-ovate "ash leaf spot" (rounded at one end and tapered at the other) may also be observed. The lesions are usually multiple, and the trunk and buttocks are most often affected. Poliosis of the scalp hair, eyebrows, or eyelashes may be seen when the underlying skin is affected. When a biopsy is performed, hypopigmented macules of TSC are found to have a reduction in the amount of epidermal melanin but a normal number of melanocytes, unlike the depigmented lesions of vitiligo and piebaldism.

A single hypopigmented macule or patch (ie, a nevus "depigmentosus") is relatively common in the general population, occurring in roughly 2% to 4% of infants or children and 5% of adults; however, ≥ 3 of these lesions are found in only 0.1% of the general population.[63] As a result, at least 3 hypomelanotic macules are required to constitute a major criterion for TSC. In addition, the minor criterion of *"confetti" lesions* refers to the presence of numerous small (1-2 mm), guttate (droplike) hypopigmented macules. Such lesions favor the extremities and are apparent in < 5% of patients with TSC.[62]

Although CALS are often noted as a feature of TSC, these lesions are seen in < 30% of patients with TSC and are usually solitary.[62] As such, this may simply reflect the prevalence of CALS in the general population.[20]

Achromic patches on the retina are analogous to the hypopigmented macules found on the skin of individuals with TSC. These "punched out" spots of retinal

Table 7 2013 revised clinical diagnostic criteria for PTEN hamartoma-tumor syndrome

Major criteria
- Multiple mucocutaneous lesions (any of the following):
- Trichilemmomas (≥3, at least 1 biopsy proven)
- Acral keratoses (≥3 papules or palmoplantar pits)
- Mucocutaneous neuromas (≥3)
- Oral papillomas, particularly on tongue and gingiva (≥3, biopsy-proven, or dermatologist-diagnosed)
- Pigmented macules on the glans penis
- Macrocephaly (>97th percentile; 58 cm in adult women, 60 cm in adult men)
- Lhermitte-Duclos disease (LDD; in an adult)
- Breast cancer
- Endometrial cancer (epithelial)
- Thyroid cancer (follicular)
- Gastrointestinal (GI) hamartomas, including ganglioneuromas but *not* hyperplastic polyps (≥3)

Minor criteria
- Vascular anomalies, including multiple intracranial developmental venous anomalies
- Lipomas (≥3)
- Testicular lipomatosis
- Autism spectrum disorder
- Mental retardation (IQ ≤ 75)
- Renal cell carcinoma
- Colon cancer
- Esophageal glycogenic acanthosis
- Thyroid cancer (papillary or follicular variant of papillary)
- Thyroid structural lesions (eg, adenoma, multinodular goiter)

Operational diagnosis in an individual:
3 major criteria including macrocephaly, LDD, or GI hamartomas –*or*–2 major criteria + 3 minor criteria

Operational diagnosis when a family member meets diagnostic criteria or has a *PTEN* mutation:
2 major criteria –*or*– 1 major + 2 minor criteria –*or*– 3 minor criteria

Adapted from Pilarski et al.[90]

depigmentation are present in up to 40% of TSC patients.[64,65] Other ocular pigmentary changes that can be seen in TSC include iris depigmentation.[66]

Hamartomatous lesions

Hamartomatous mucocutaneous lesions in patients with TSC have a predilection for the cephalic region, where mesenchymal tissues are derived from the neural crest, as well as the lower back, ungual area, and occasionally flexural sites. Facial *angiofibromas* (previously known by the misnomer "adenoma sebaceum") are the second most common cutaneous manifestation of TSC. They typically begin to appear between 2 and 5 years of age and develop by adolescence in ~75% of patients.[62] In contrast, facial angiofibromas associated with multiple endocrine neoplasia type 1 or Birt-Hogg-Dubé syndrome tend to have onset in adulthood. Of note, connective tissue nevi, gingival papules, and confetti-like hypomelanotic macules may also be seen in multiple endocrine neoplasia type 1.

TSC-associated angiofibromas classically present as smooth, dome-shaped, pink-to-red papules and nodules (Figure 4B). They are distributed bilaterally over the central face, with the occasional exception of unilateral involvement in patients with mosaic TSC. Angiofibromas often start as erythematous macules, becoming more elevated and sometimes coalescing over time. Eyelid involvement is seen in ~40% of patients.[64] *Fibrous cephalic plaques* favor the forehead but can occur in other facial sites (Figure 4C). These lesions, which represent larger variants of the angiofibroma, are evident in ~25% of patients with TSC. Histologically, angiofibromas and fibrous plaques feature a dermal proliferation of fibroblasts and dilated blood vessels in a collagenous stroma with concentric perifollicular fibrosis.

Ungual fibromas (Koenen tumors) may be considered as an acral counterpart to facial angiofibromas. The prevalence of these lesions in TSC patients increases with age, from 15% to 20% in children[62,67] to 80% in adults.[68] Skin-colored to pink papules, which often have tapered or hyperkeratotic tips, are commonly found on multiple digits (Figure 4D). Periungual fibromas (originating from the proximal or lateral nail fold) predominate on the feet (especially the fifth toe) and may be associated with a longitudinal groove in the nail plate. Of note, similar grooves sometimes occur without a

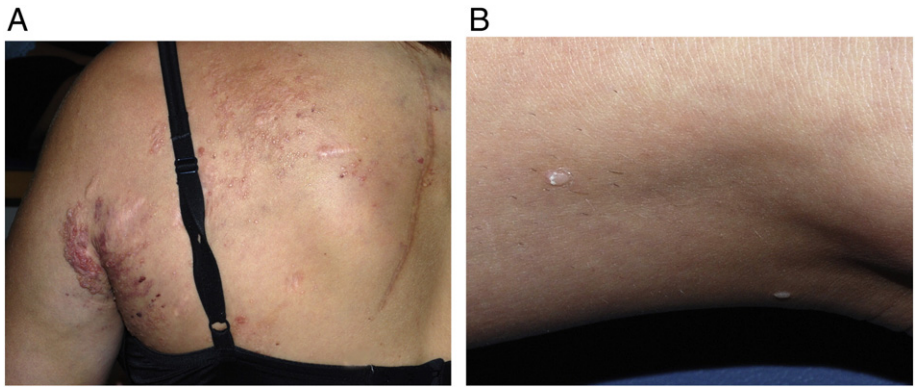

Fig. 5 Skin findings in PTEN hamartoma-tumor syndrome. A, Vascular malformation with lymphatic and arteriovenous components, associated with soft tissue overgrowth. B, Subtle keratotic papules on the ankle.

visible fibroma. In contrast, subungual fibromas (originating under the nail plate) and "red comets" (blanchable longitudinal red streaks with proximal narrowing) favor the hands (especially the thumb). Splinter hemorrhages and longitudinal leukonychia may also be observed.[68] The distribution of ungual lesions suggests that repetitive trauma represents a pathogenic factor.

Molluscum pendulum are angiofibroma variants that occur in flexural sites and resemble large skin tags.

The *shagreen patch* is a specific type of connective tissue nevus that usually becomes evident during the first decade of life, eventually affecting approximately half of patients with TSC.[62,69] These skin-colored to yellowish-brown or pink, slightly elevated plaques favor the lumbosacral area (Figure 4E). They have a characteristic *peau d'orange* or pigskin-like texture with prominent, slightly depressed follicular orifices.

The oral manifestations of TSC can be useful in establishing the diagnosis. *Intraoral fibromas* affect 20% to 70% of patients, with a higher prevalence in adults than children. These papules are most often located on the gingiva, but they can also occur in buccal, labial, and other sites.[70] *Multiple dental enamel pits* are present in >95% of adults with TSC, compared with ≤7% of individuals in the general population.[71]

Retinal hamartomas with astrocytic histology similar to that of cortical tubers are found in 30% to 50% of patients with TSC.[64,72] These lesions are often present in young children and can represent a useful diagnostic marker. Morphologic subtypes of retinal hamartomas include: (1) flat, translucent lesions; (2) opaque, multinodular, calcified "mulberry" lesions; and (3) transitional lesions with overlapping features.[64] Although retinal hamartomas do not usually lead to visual loss, they are associated with an increased risk of subependymal giant cell astrocytomas, renal angiomyolipomas, cognitive impairment, and epilepsy.[73] Retinal astrocytomas with more aggressive behavior and hamartomas of the iris and ciliary body are also occasionally observed in patients with TSC.

Other hamartomatous manifestations of TSC

Involvement of the CNS with hamartomatous lesions represents the greatest source of morbidity and mortality in patients with TSC. MRI of the brain shows multiple cortical tubers (a form of cortical dysplasia) and subependymal nodules (often calcified) in 80% to >90% of TSC patients before 2 years of age, and the severity of brain involvement may correlate with seizure activity and intellectual deficits. Infantile spasms affect ~70% of TSC patients, typically beginning at 3 to 6 months of age, and other forms of epilepsy often develop later in childhood. Cognitive impairment, autism spectrum disorders, and neuropsychiatric conditions are common, although the degree of disability varies considerably. Subependymal giant cell astrocytomas with more aggressive behavior can also develop, most often during childhood.

Other systemic findings in TSC (see Table 6) result from benign hamartomatous growths that may be asymptomatic or highly problematic, depending on their location and size. Cardiac rhabdomyomas, one of the earliest and most specific manifestations of TSC, have great diagnostic utility. These lesions are present in >80% of infants with TSC and are often detected prenatally. Fortunately, they only occasionally disrupt cardiac function and tend to regress over time. Pulmonary lymphangioleiomyomatosis affects 30% to 40% of young women with TSC and can result in progressive dyspnea on exertion and recurrent pneumothoraces. Renal angiomyolipomas are found in 75% to 90% of TSC patients and sometimes lead to renal failure.

Advances in the management of TSC

Guidelines for surveillance and management of patients with TSC have recently been published.[74] The discovery of the relationship between hamartin/tuberin and the mTOR pathway has led to great advances in the management of tuberous sclerosis via use of mTOR inhibitors such as sirolimus (rapamycin) and everolimus. Large clinical trials have found that oral administration of these agents is beneficial for renal angiomyolipomas, pulmonary lymphangioleiomyomatosis, and subependymal giant cell astrocytomas.[75–78]

After the observation that facial angiofibromas regress in TSC patients receiving systemic sirolimus,[79] topical application of this medication has been successfully employed to treat these lesions (as well as fibrous plaques and hypomelanotic macules) without systemic absorption.[80–83] Sirolimus concentrations of <0.1% to 1% have been used, with more irritation produced by the commercially available 0.1% solution (Rapamune® 1 mg/mL) than ointment and gel formulations.[81,83] Reduced erythema and flattening are typically seen within 3 months of initiating topical therapy of angiofibromas, with the most dramatic improvement in children ≤10 years of age. Although relapses occur upon discontinuation, maintenance via decreasing from daily to thrice weekly application has been described.[81,83]

PTEN hamartoma-tumor syndrome

The PTEN hamartoma-tumor syndrome (PHTS) encompasses a spectrum of disorders caused by loss-of-function germline mutations in the phosphatase and tensin homolog *(PTEN)* tumor suppressor gene. *Cowden syndrome* and *Bannayan-Riley-Ruvalcaba syndrome*, autosomal dominant genodermatoses with overlapping features, are included in this group. PHTS is characterized by hamartomatous overgrowth in a variety of organ systems, with prominent

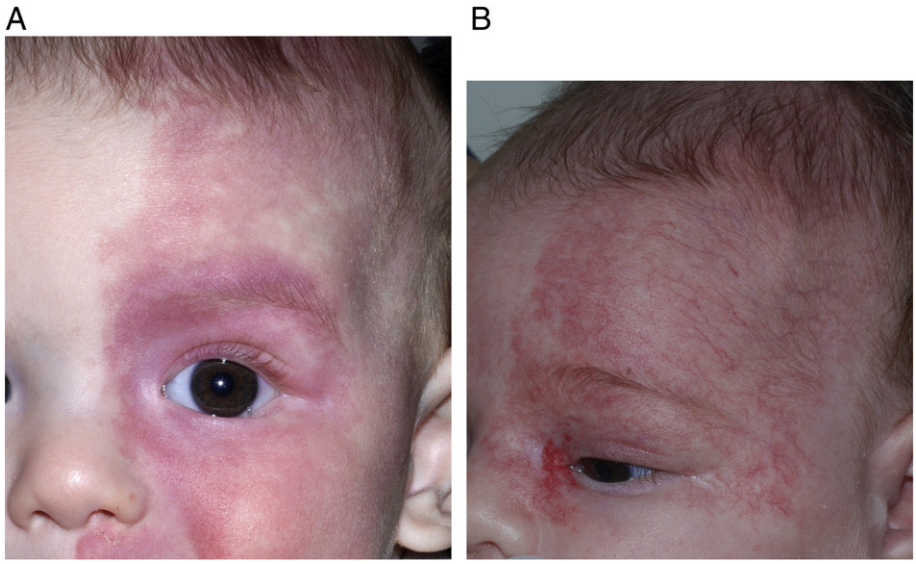

Fig. 6 Port-wine stain versus segmental infantile hemangioma. A, This infant with a blotchy pink port-wine stain involving the V1 and V2 distributions is at risk for Sturge-Weber syndrome. B, Minimal-growth segmental infantile hemangioma, *not* a port-wine stain. Clues to the diagnosis include the prominent telangiectasias and slightly elevated red papules at the medial canthus. This infant is at risk for PHACE syndrome.

manifestations in the skin and brain. Ocular findings also occur in PHTS and can represent clues to the diagnosis.

The *PTEN* gene encodes a lipid phosphatase that negatively regulates the phosphatidylinositol 3-kinase (PI3 K)/AKT pathway (see Figure 1). Signaling via PI3 K/AKT, which inhibits the tuberin tumor suppressor protein, is therefore increased in patients with PHTS. As in tuberous sclerosis, this results in elevated mTOR activity that promotes cell growth and survival (see earlier). Recently, gain-of-function germline mutations in the *PIK3 CA* or *AKT1* gene were found in a subset of patients with a Cowden syndrome phenotype but no *PTEN* mutation.[84]

Somatic loss of PTEN function is associated with a wide array of sporadic human cancers,[85] including those of neural lineage.[86–88] PTEN also plays an important role in the development of the CNS. Homozygous deletion of *PTEN* during murine embryogenesis leads to enlarged, architecturally disordered brains with increased cell survival, size, and proliferation.[89] This explains the high frequency of macrocephaly in individuals with PHTS.

Revised, evidence-based diagnostic criteria for PHTS were proposed in 2013 (Table 7).[90] Goals included increasing specificity and incorporating recently recognized clinical manifestations. Genetic testing can help to confirm the diagnosis of PHTS and identify affected family members.[91]

Cutaneous and oral manifestations of PHTS

The skin findings that characterize the Bannayan-Riley-Ruvalcaba syndrome phenotype usually become apparent by early childhood. They include *pigmented macules of the genitalia* (penis > vulva), *lipomas*, and *vascular anomalies* with a fast-flow component (Figure 5A). More severely affected PHTS patients with a *PTEN* "second hit" that occurs during embryonic development may be born with prominent mosaic manifestations resembling Proteus syndrome, such as *segmental overgrowth*, *verrucous epidermal nevi*, and deformities related to lipomatosis and vascular malformations; however, true Proteus syndrome is caused by mosaicism for activating *AKT1* mutations, and patients with mosaic *PIK3 CA* mutations can also have similar findings. *Mucocutaneous neuromas* have recently been added as a major diagnostic criterion for PHTS (see Table 7).[90] These lesions often arise during childhood and present as skin-colored to pink, dome-shaped papules on the extremities and face.[92]

In contrast, the classic mucocutaneous hallmarks of Cowden syndrome typically develop during the second or third decade of life. *Trichilemmomas* and other verrucous papules favor the face and ears, *keratoses* are seen in acral locations (Figure 5B), and *sclerotic fibromas* appear as skin-colored to whitish, firm papules.[93] *Oral papillomas*, which can represent fibromas or (less commonly) glycogenic acanthosis, most often occur on the tongue, gingiva, and lips; multiple lesions may lead to a cobblestone-like texture.

Ocular manifestations of PHTS

Corneal nerve hypertrophy is evident in approximately one third of patients with Bannayan-Riley-Ruvalcaba syndrome. Like mucocutaneous neuromas, this finding is shared with multiple endocrine neoplasia type 2 B (MEN2 B). Children

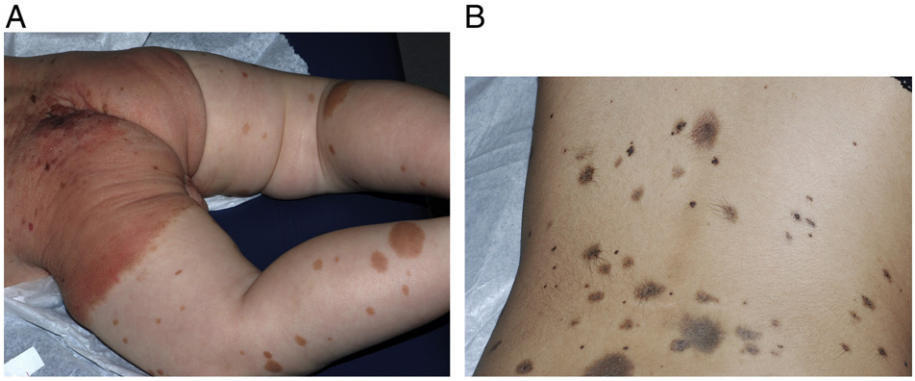

Fig. 7 Patients at risk for neurocutaneous melanocytosis. A, Multiple satellite nevi associated with a giant congenital melanocytic nevus in a "bathing trunk" distribution. B, Numerous small and medium-sized congenital melanocytic nevi without a large "mother ship" nevus.

with PHTS may also have prominent Schwalbe lines, pseudopapilledema, downward-slanting palpebral fissures, amblyopia, and strabismus.[94,95] Other ocular features that have been reported in patients with PHTS include myopia, angioid streaks, and cataracts.

Other manifestations of PHTS

Macrocephaly, one of the most consistent features of PHTS, is present in ≥80% of affected individuals.[90] Intracranial developmental venous anomalies are also commonly observed when a brain MRI is performed. Less common neurologic manifestations include developmental delay, autism, seizures, and hypotonia. *Lhremitte-Duclos disease*, a hamartomatous dysplastic gangliocytoma of the cerebellum, occurs in a minority of young adults with PHTS.

Patients with PHTS have increased risk for the development of malignancy, particularly breast (25%->50% of women), thyroid, endometrial, colon, and renal carcinomas. Hamartomatous changes can also develop in a variety of organs (see Table 7).

Advances in the management of PHTS

Guidelines for cancer surveillance in patients with PHTS have been proposed.[96,97] Treatment with sirolimus has been reported to improve vascular and lipomatous lesions of PHTS.[98,99] Clinical trials are in progress to further investigate the utility of mTOR inhibitors in PHTS.

Sturge-Weber syndrome

Sturge-Weber syndrome (SWS) is a sporadic neurocutaneous disorder characterized by a facial port-wine stain (PWS) associated with ipsilateral capillary-venous abnormalities affecting the leptomeninges (leading to seizures, intellectual disability, and/or hemiparesis) and often the choroid of the eye (leading to glaucoma).[100,101] Definitions of SWS used in the literature have varied, with some authors requiring all three components for a diagnosis of complete SWS.[102] Although patients with a PWS plus leptomeningeal involvement alone are generally diagnosed as having SWS, those with a facial PWS and glaucoma alone are usually classified separately or considered as having partial SWS.[100,103,104] Leptomeningeal and choroidal vascular anomalies have also been described in the absence of a PWS and may represent another partial variant of SWS.

The overall incidence of SWS is estimated to be between 1 in 20,000 and 50,000 live births.[105] SWS occurs almost exclusively in patients whose PWS involves the distribution of the ophthalmic (V1) branch of the trigeminal nerve. This region includes the forehead, mid-nose, upper eyelids, and sometimes a "watershed" area on the lower eyelids that may also be innervated by V2.[100,101,104,106] SWS occurs in ≤10% of patients with a unilateral PWS affecting only a portion of the V1 distribution, with the upper eyelid representing the highest-risk site within this region. The incidence of SWS increases to 25% to >50% in those with a PWS affecting the entire V1 region, with greatest likelihood if bilateral or together with the V2 and V3 involvement.[100,101,104,106]

It has long been hypothesized that both PWSs and SWS are caused by mosaicism for a somatic mutation, with the clinical manifestations depending on the timing and location of the mutational event in the developing embryo. An earlier mutation in a progenitor cell would therefore result in a larger field of anomalies and potentially affect regional tissues beyond the skin. Of note, cephalic neural crest–derived cells destined to form the tissues involved in SWS—nasofrontal facial skin (including pericytes and smooth muscle of blood vessels), ocular choroid, and pia mater (especially in the parieto-occipital area)—all arise from the same embryonic region.[100,102,104] A somatic activating missense mutation in the *GNAQ* gene (Arg183 Gln) was recently identified in affected tissues (both skin and brain) in 88% (23/26) of patients with SWS as well as in the

skin in 92% (12/13) patients with nonsyndromic PWSs.[107] This gene encodes the Q-class G protein α-subunit, activation of which increases MAPK signaling (see Figure 1).

A different *GNAQ* mutation (Gln209 Leu) that produces more robust MAPK upregulation is found in uveal melanomas, blue nevi, and nevus of Ota melanocytes.[108] Interestingly, dermal melanocytosis (including nevus of Ota with potential ocular involvement) and PWSs occur together as "twin spots" in patients with *phakomatosis pigmentovascularis* (PPV), which can be associated with uveal melanoma.[109] PPV thus presumably reflects the effects of same *GNAQ* mutation in different cell types (melanocytic and vascular).

Cutaneous manifestations of SWS

The cutaneous hallmark of SWS is a *facial PWS*, a capillary malformation that presents at birth as a pinkish-red patch with a unilateral > bilateral segmental distribution (Figure 6A). The differential diagnosis may include a stage 1 arteriovenous malformation (warm, favors the central face) and an early or minimal-growth segmental infantile hemangioma (prominent telangiectasias ± peripheral red papules; Figure 6B). Facial PWSs must also be distinguished from the more common nevus simplex (salmon patch) that presents as congenital vascular "stain(s)" on the mid-face (forehead, glabella, nasal tip, philtrum), eyelids, occiput, and/or nape ("stork bite"). These lesions are not associated with extracutaneous manifestations and tend to fade between 1 and 3 years of age, especially when located on the face. In contrast, PWSs persist. By late adolescence or adulthood, they commonly develop a darker red-purple color and become thicker, often with superimposed nodularity.[105] Other findings that may be associated with a PWS involving the V2 or V3 region include maxillary overgrowth, macrocheilia, gingival hypertrophy, and dental abnormalities. This reflects the common origin of facial connective tissue and bones as well as dental papillae from the neural crest.

Treatment of facial PWSs with a pulsed-dye laser (PDL) during infancy can prevent the potential psychosocial sequelae of this highly visible birthmark. Approximately 6 to 10 PDL sessions at intervals of 2 to 4 weeks are generally required,[110] and early initiation of therapy helps to avoid lesional thickening and maximize efficacy. Overall, approximately three fourths of facial PWSs improve substantially with PDL treatment, with lesions located on the central face tending to be more resistant than those in other sites. PDL treatment is safe in infants and children of all ages, producing short-lived purpura and a low risk of temporary hypo- or hyperpigmentation or (less often) scarring. Although such side effects are more common in individuals with darkly pigmented skin (eg, skin type V), these patients can have a good response and should not be excluded from treatment.[111]

Ocular manifestations of SWS

The most common ocular manifestation of SWS is *glaucoma*. It occurs in approximately 15% to 20% of individuals with a PWS in the V1 and/or V2 region, with a higher likelihood if the PWS affects both the upper and lower eyelids or is bilateral. Additional risk factors for glaucoma in patients with a facial PWS include episcleral involvement, evidence of a choroidal vascular malformation on funduscopic examination, iris heterochromia, and neurologic findings of SWS.[103] PWS-associated glaucoma is congenital or develops during the first 2 years of life in approximately 60% of affected individuals, and this can lead to buphthalmos (enlargement of the globe).[112] A large, cloudy cornea in an infant can be a sign of acute glaucoma, which represents an ophthalmologic emergency. In contrast, PWS-associated glaucoma with onset in later childhood or early adulthood typically presents with painless, progressive visual field loss.[113]

Several pathogenic mechanisms for PWS-associated glaucoma have been proposed. Recent use of enhanced depth imaging spectral-domain optical coherence tomography (SD-OCT) in SWS patients has enabled detection of choroidal abnormalities that are not visible via funduscopic examination.[114] Early-onset glaucoma may result from the choroidal malformation and related trabecular dysgenesis, leading to mechanical obstruction of the angle of the eye.[112,115] In later-onset glaucoma, increased episcleral venous pressure and premature degenerative changes of the trabecular network/Schlemm canal are thought to play a role.[103,116]

Glaucoma can be a major source of morbidity in patients with periocular PWSs, and early initiation of treatment is critical in improving visual outcomes. Considering the substantial risk of congenital glaucoma, an initial ophthalmologic evaluation should be performed in the neonatal period. Lifelong monitoring is recommended, with ophthalmologic examinations every 3 to 6 months during the first 2 years of life, and then at least yearly.[102,103] Medical therapy is generally initiated for PWS-associated glaucoma, but surgical interventions such as trabeculotomy or trabeculectomy are often required, especially for early-onset disease. Of note, there is no evidence that PDL treatment of periocular PWSs worsens glaucoma or increases the risk of its development.[112]

Other manifestations of SWS

Neurologic manifestations represent the greatest cause of morbidity in SWS. *Seizures* are the most common clinical finding, occurring in ~70% to 80% of affected individuals[106,117] and most often developing during the first year of life. *Cognitive impairment* is noted in approximately half of SWS patients and ranges from mild learning disabilities to severe mental retardation. Other possible neurologic sequelae include *hemiparesis* (contralateral to the PWS) and *visual field defects*, both of which may occur in transient strokelike episodes, as well as behavioral problems, headaches, and

endocrine dysfunction due to effects on the hypothalamic-pituitary axis (eg, growth hormone deficiency).

Neuroimaging can help to establish the diagnosis of SWS and evaluate the extent of intracranial involvement. MRI using a combination of gadolinium-enhanced scans and susceptibility-weighted imaging (SWI) is recommended for the initial evaluation of infants and children with SWS.[118,119] This can show characteristic findings such as cortical calcifications, enlargement of the choroid plexus, and abnormalities in leptomeningeal, periventricular, and transmedullary veins.[118] Diffusion- and perfusion-weighted MRI may also be used to assess effects on the brain parenchyma. Of note, MRI performed in the first few months to year of life is less sensitive in detecting manifestations of SWS.[105]

Early recognition and aggressive control of seizures is a key component in the management of SWS patients, and refractory epilepsy may require surgical intervention.[118] Because venous congestion and thrombosis contribute to progressive brain injury in SWS, low-dose aspirin may be of benefit, especially in patients with strokelike episodes[118,120,121]; however, whether prophylactic administration of low-dose aspirin and/or anticonvulsants to presymptomatic patients with extensive brain involvement improves prognosis remains to be determined.[118–121]

Neurocutaneous melanocytosis

Neurocutaneous melanocytosis (NCM) refers to proliferation of melanocytes in the CNS as well as the skin in patients with congenital melanocytic nevi (CMN). Melanocytes are physiologically present in the pia mater of the meninges, which is the primary site of brain involvement in NCM. Individuals with both cutaneous and CNS melanomas are excluded from diagnosis of NCM due to the possible metastatic origin of the brain lesions.[122]

As noted for SWS (see earlier), mosaicism for a mutation arising in a neuroectodermal progenitor cell during early embryogenesis could lead to a broad distribution of skin lesions (eg, numerous and/or large CMN) and involvement of extracutaneous tissues.[123] Recently, the same somatic activating mutation in codon 61 of the *NRAS* gene was identified in multiple different CMN and brain lesions of individual patients with NCM but not in unaffected tissues or blood.[124] Activated NRAS signals through both MAPK and PI3 K/AKT pathways (see Figure 1), in contrast to stimulation of only the MAPK pathway by the activated BRAF found in most small CMN. In addition to increasing cell proliferation, the PI3 K/AKT pathway promotes melanocyte survival and directional migration, which may contribute to the large and widespread melanocytic lesions observed in NCM.

Congenital melanocytic nevi: Risk factors for NCM

The presence of *numerous CMN*, regardless of whether or not there is "mother ship" large CMN (defined as final size >20 cm), represents the most important risk factor for NCM (Figure 7). Approximately two thirds of patients with NCM have a large CMN accompanied by "satellite" nevi, and one third of patients have many small to medium-sized CMN (generally >10 lesions).[122,125] Among individuals with a large CMN, those with >20 satellite nevi have a fivefold higher risk of NCM compared with those with ≤20 satellites.[126] An increased risk of NCM has also been noted in patients with CMN that have a final size of >40 cm or (in some studies) a posterior axial location.

Ocular findings in patients with NCM

NCM does not typically have ocular manifestations. In addition to ocular signs of increased intracranial pressure (eg, papilledema), uveal coloboma-like lesions and alterations in the retinal pigment epithelium have been reported.[127] A constellation of findings referred to as SCALP syndrome includes a *s*ebaceous nevus, *C*NS malformations, *a*plasia cutis congenita, limbal dermoid, and *p*igmented CMN.[128]

Neurologic manifestations of NCM

NCM is divided into symptomatic and asymptomatic forms, with the latter representing patients whose brain involvement is detected via MRI screening. MRI findings of NCM can include areas of brain parenchyma (especially the temporal lobes/amygdala) with increased T1 signal, gadolinium enhancement of diffusely thickened meninges, and obvious masses.[129,130] CNS abnormalities such as the Dandy-Walker malformation, posterior fossa cysts, and intraspinal lipomas are occasionally evident.

Symptomatic NCM occurs in approximately 4% of patients with high-risk CMN, and the prognosis is poor even in the absence of melanoma. Patients typically present with hydrocephalus, seizures, and signs of increased intracranial pressure (eg, vomiting, headache). Symptoms develop at a median age of 2 years, although individuals with a discrete intracranial mass tend to become symptomatic later (median age, ~10 years) and are more likely to have focal sensorimotor deficits.[131] Neurologic manifestations such as developmental delay and abnormal tone are observed ~15% of children with high-risk CMN, including a subset of those with normal brain MRIs.[132]

Asymptomatic NCM can be diagnosed based on MRI-evidence of CNS melanosis in 5% to 25% of infants and children with high-risk CMN.[129,132,133] Due to the paucity of longitudinal studies, the proportion of these patients destined to become symptomatic from NCM is unknown. In one series, 10 patients with asymptomatic NCM diagnosed at a mean age of 6 months were followed for 5 years, and only 1 individual developed neurologic symptoms.[133]

Screening for and management of NCM

Infants at risk for NCM can be screened with MRI of the brain and spine. Sensitivity is maximized if imaging is performed during the first 4 to 6 months of life, before myelination that may obscure evidence of melanosis, and gadolinium enhancement can help to visualize thickened meninges.[129,133] At-risk patients should also be followed with serial neurologic examinations and developmental assessments.

Patients with clinical or MRI evidence of NCM may benefit from referral to a pediatric neurologist and, in some instances, a neurosurgeon. In one study, more than one third of CMN patients with abnormal MRI findings required surgical intervention.[132] For patients with asymptomatic NCM, repeat MRI studies are indicated if clinical manifestations develop and otherwise on an approximately annual basis, with adjustments depending on the severity and progression of the MRI findings.[134] A treatment strategy targeting both MAPK (eg, MEK inhibitors) and PI3 K/mTOR (eg, sirolimus) pathways could have benefit in patients with symptomatic NCM.[135]

References

1. Sarnat HB, Flores-Sarnat L. Embryology of neurocutaneous syndromes: role of neural crest. In: Neurocutaneous Syndromes during Development. London, UK: John Libbey Eurotext. 2005.
2. Sarnat HB, Flores-Sarnat L. Embryology of the neural crest: its inductive role in the neurocutaneous syndromes. *J Child Neurol.* 2005;20:637-643.
3. Le Dourarin N, Kalcheim C. *The Neural Crest.* 2nd ed. Cambridge, UK: Cambridge University Press. 1999.
4. Hall BK. *The Neural Crest in Development and Evolution.* New York, NY: Springer-Verlag. 1999.
5. Huson SM, Compston DA, Clark P, Harper PS. A genetic study of von Recklinghausen neurofibromatosis in south east Wales. I. Prevalence, fitness, mutation rate, and effect of parental transmission on severity. *J Med Genet.* 1989;26:704-711.
6. Samuelsson B, Axelsson R. Neurofibromatosis. A clinical and genetic study of 96 cases in Gothenburg, Sweden. *Acta Derm Venereol Suppl.* 1981;96:67-71.
7. Skolnick MH, Ponder B, Seizinger B. Linkage of NF1 to 12 chromosome 17 markers: a summary of eight concurrent reports. *Genomics.* 1987;1:382-383.
8. Wigler MH. Oncoproteins. GAPs in understanding Ras. *Nature.* 1990;346:696-697.
9. Stocker KM, Baizer L, Coston T, Sherman L, Ciment G. Regulated expression of neurofibromin in migrating neural crest cells of avian embryos. *J Neurobiol.* 1995;27:535-552.
10. Maertens O, De Schepper S, Vandesompele J, et al. Molecular dissection of isolated disease features in mosaic neurofibromatosis type 1. *Am J Hum Genet.* 2007;81:243-251.
11. National Institutes of Health Consensus Development Conference Statement: Neurofibromatosis. Bethesda, Md., USA, July 13-15, 1987, 1. *Neurofibromatosis*; 1988. p. 172-178.
12. DeBella K, Szudek J, Friedman JM. Use of the National Institutes of Health criteria for diagnosis of neurofibromatosis 1 in children. *Pediatrics.* 2000;105:608-614.
13. Tsang E, Birch P, Friedman JM. Valuing gene testing in children with possible neurofibromatosis 1. *Clin Genet.* 2012;82:591-593.
14. Van Minkelen R, van Bever Y, Kromosoeto J, et al. A clinical and genetic overview of 18 years neurofibromatosis type 1 molecular diagnostics in the Netherlands. *Clin Genet.* 2014;85:318-327.
15. Burkitt Wright EM, Sach E, Sharif S, et al. Can the diagnosis of NF1 be excluded clinically? A lack of pigmentary findings in families with spinal neurofibromatosis demonstrates a limitation of clinical diagnosis. *J Med Genet.* 2013;50:606-613.
16. Nunley KS, Gao F, Albers AC, Bayliss SJ, Gutmann DH. Predictive value of café au lait macules at initial consultation in the diagnosis of neurofibromatosis type 1. *Arch Dermatol.* 2009;145:883-887.
17. Duong TA, Bastuji-Garin S, Valeyrie-Allanore L, Sbidian E, Ferkal S, Wolkenstein P. Evolving pattern with age of cutaneous signs in neurofibromatosis type 1: a cross-sectional study of 728 patients. *Dermatology.* 2011;222:269-273.
18. Boyd KP, Korf BR, Theos A. Neurofibromatosis type 1. *J Am Acad Dermatol.* 2009;61:1-14.
19. De Schepper S, Boucneau J, Lambert J, Messiaen L, Naeyaert JM, Lambert J. Café-au-lait spots in neurofibromatosis type 1 and in healthy control individuals: hyperpigmentation of a different kind? *Arch Dermatol Res.* 2006;297:439-449.
20. Landau M, Krafchik BR. The diagnostic value of café-au-lait macules. *J Am Acad Dermatol.* 1999;40:877-890.
21. Carcavilla A, Pinto I, Muñoz-Pacheco R, Barrio R, Martin-Frías M, Ezquieta B. LEOPARD syndrome (PTPN11, T468 M) in three boys fulfilling neurofibromatosis type 1 clinical criteria. *Eur J Pediatr.* 2011;170:1069-1074.
22. Yeung JT, Pollack IF, Shah S, Jaffe R, Nikiforova M, Jakacki RI. Optic pathway glioma as part of a constitutional mismatch-repair deficiency syndrome in a patient meeting the criteria for neurofibromatosis type 1. *Pediatr Blood Cancer.* 2013;60:137-139.
23. Messiaen L, Yao S, Brems H, et al. Clinical and mutational spectrum of neurofibromatosis type 1-like syndrome. *JAMA.* 2009;302:2111-2118.
24. Stevens CA, Chiang PW, Messiaen LM. Café-au-lait macules and intertriginous freckling in piebaldism: clinical overlap with neurofibromatosis type 1 and Legius syndrome. *Am J Med Genet A.* 2012;158(A):1195-1199.
25. Wimmer K, Etzler J. Constitutional mismatch repair-deficiency syndrome: have we so far seen only the tip of an iceberg? *Hum Genet.* 2008;124:105-122.
26. Stowe IB, Mercado EL, Stowe TR, et al. A shared molecular mechanism underlies the human rasopathies Legius syndrome and neurofibroamtosis-1. *Genes Dev.* 2012;26:1421-1426.
27. Zeller J, Wechsler J, Revuz J, Wolkenstein P. Blue-red macules and pseudoatrophic macules in neurofibromatosis 1. *Ann Dermatol Venereol.* 2002;129:180-181.
28. Staser K, Yang FC, Clapp DW. Mast cells and the neurofibroma microenvironment. *Blood.* 2010;116:157-164.
29. Zvulunov A, Esterly NB. Neurocutaneous syndromes associated with pigmentary skin lesions. *J Am Acad Dermatol.* 1995;32:915-935.
30. Schaffer JV, Chang MW, Kovich OI, Kamino H, Orlow SJ. Pigmented plexiform neurofibroma: distrinction from a large congenital melanocytic nevus. *J Am Acad Dermatol.* 2007;56:862-868.
31. Schnur RE. Type I, neurofibromatosis: a geno-oculo-dermatologic update. *Curr Opin Ophthalmol.* 2012;23:364-372.
32. Stewart DR, Sloan JL, Yao L, et al. Diagnosis, management and complications of glomus tumours of the digits in neurofibromatosis type 1. *J Med Genet.* 2010;47:525-532.
33. Brems H, Park C, Maertens O, et al. Glomus tumors in neurofibromatosis type 1: genetic, functional, and clinical evidence of a novel association. *Cancer Res.* 2009;69:7393-7401.
34. Ferrari F, Masurel A, Olivier-Faivre L, Vabres P. Juvenile xanthogranuloma and nevus anemicus in the diagnosis of neurofibromatosis type 1. *JAMA Dermatol.* 2014;150:42-46.

35. Marque M, Roubertie A, Jaussent A, et al. Nevus anemicus in neurofibromatosis type 1: a potential new diagnostic criterion. *J Am Acad Dermatol.* 2013;69:768-775.
36. Harrison B, Moore AM, Calfee R, Sammer DM. The association between glomus tumors and neurofibromatosis. *J Hand Surg [Am].* 2013;38:1571-1574.
37. Cambiaghi S, Restano L, Caputo R. Juvenile xanthogranuloma associated with neurofibromatosis 1: 14 patients without evidence of hematologic malignancies. *Pediatr Dermatol.* 2004;21:97-101.
38. Nichols JC, Amato JE, Chung SM. Characteristics of Lisch nodules in patients with neurofibromatosis type 1. *J Pediatr Ophthalmol Strabismus.* 2003;40:293-296.
39. Richetta A, Giustini S, Recupero SM, et al. Lisch nodules of the iris in neurofibromatosis type 1. *JEADV.* 2004;18:342-344.
40. Williamson TH, Garner A, Moore AT. Structure of Lisch nodules in neurofibromatosis type 1. *Ophthalmic Paediatr Genet.* 1991;12: 11-17.
41. Listernick R, Charrow J, Greenwald MJ, Esterly NB. Optic gliomas in children with neurofibromatosis type 1. *J Pediatr.* 1989;114:788-792.
42. Listernick R, Ferner RE, Liu GT, Gutmann DH. Optic pathway gliomas in neurofibromatosis-1: controversies and recommendations. *Ann Neurol.* 2007;61:189-198.
43. Czyzyk E, Jóźwiak S, Roszkowski M, Schwartz RA. Optic pathway gliomas in children with and without neurofibromatosis 1. *J Child Neurol.* 2003;18:471-478.
44. Laue L, Comite F, Hench K, Loriaux L, Cutler GB, Pescovitz OH. Precocious puberty associated with neurofibromatosis and optic gliomas. *Am J Dis Child.* 1985;139:1097-1100.
45. Cassiman C, Legius E, Spileers W, Casteels I. Ophthalmological assessment of children with neurofibromatosis type 1. *Eur J Pediatr.* 2013;172:1327-1333.
46. Avery RA, Hwang EI, Jakacki RI, Packer RJ. Marked recovery of vision in children with optic pathway gliomas treated with bevacizumab. *JAMA Ophthalmol.* 2014;132:111-114.
47. Yasunari T, Shiraki K, Hattori H, Miki T. Frequency of choroidal abnormalities in neurofibromatosis type 1. *Lancet.* 2000;356:988-992.
48. Viola F, Villani E, Natacci F, et al. Choroidal abnormalities detected by near-infrared reflectance imaging as new diagnostic criterion for neurofibromatosis 1. *Ophthalmology.* 2012;119:369-375.
49. Shields JA, Pellegrini M, Kaliki S, Mashayekhi A, Shields CL. Retinal vasoproliferative tumors in 6 patients with neurofibromatosis type 1. *JAMA Ophthalmol.* 2014;132:190-196.
50. Levine TM, Materek A, Abel J, O'Donnell M, Cutting LE. Cognitive profile of neurofibromatosis type 1. *Semin Pediatr Neurol.* 2006;13: 8-20.
51. Ferner RE, Huson SM, Thomas N, et al. Guidelines for the diagnosis and management of individuals with neurofibromatosis 1. *J Med Genet.* 2007;44:81-88.
52. Williams VC, Lucas J, Babcock MA, Gutmann DH, Korf B, Maria BL. Neurofibromatosis type 1 revisited. *Pediatrics.* 2009;123: 124-133.
53. Yang FC, Ingram DA, Chen S, et al. Nf1-dependent tumors require a microenvironment containing Nf1 +/– and c-kit dependent bone marrow. *Cell.* 2008;135:437-448.
54. Robertson KA, Nalepa G, Yang FC, et al. Imatinib mesylate for plexiform neurofibromas in patients with neurofibromatosis type 1: A phase 2 trial. *Lancet Oncol.* 2012;13:1218-1224.
55. Jessen WJ, Miller SJ, Jousma E, et al. MEK inhibition exhibits efficacy in human and mouse neurofibromatosis tumors. *J Clin Invest.* 2013;123:340-347.
56. O'Callaghan F, Shiell A, Osborne J, Martyn C. Prevalence of tuberous sclerosis estimated by capture-recapture analysis. *Lancet.* 1998;352: 318-319.
57. Osborne JP, Fryer A, Webb D. Epidemiology of tuberous sclerosis. *Ann N Y Acad Sci.* 1991;615:125-127.
58. Dabora SL, Jóźwiak S, Franz DN, et al. Mutational analysis in a cohort of 224 tuberous sclerosis patients indicated increased severity of TSC2, compared with TSC1, disease in multiple organs. *Am J Hum Genet.* 2001;68:64-80.
59. Curatolo P, Bombardieri R, Jóźwiak S. Tuberous sclerosis. *Lancet.* 2008;372:657-668.
60. Napolioni V, Moavero R, Curatolo P. Recent advances in neurobiology of tuberous sclerosis complex. *Brain Dev.* 2009;31:104-113.
61. Curran MP. Everolimus: in patients with subependymal giant cell astrocytoma associated with tuberous sclerosis complex. *Paediatr Drugs.* 2012;14:51-60.
62. Jóźwiak S, Goodman M, Lamm SH. Poor mental development in patients with tuberous sclerosis complex: clinical risk factors. *Arch Neurol.* 1998;55:379-384.
63. Fitzpatrick TB. History and significance of white macules, earliest visible sign of tuberous sclerosis. *Ann N Y Acad Sci.* 1991;615:26-35.
64. Rowley S, O'Callagan F, Osborne J. Ophthalmic manifestations of tuberous sclerosis: a population based study. *Br J Ophthalmol.* 2001;85:420-423.
65. Shields CL, Reichstein DA, Bianciotto C, Shields JA. Retinal pigment epithelial depigmented lesions associated with tuberous sclerosis complex. *Arch Opththalmol.* 2012;130:387-390.
66. Lucchese NJ, Goldberg MF. Iris and fundus pigmentary changes in tuberous sclerosis. *J Pediatr Ophthalmol Strabismus.* 1981;18:45-46.
67. Northrup H, Krueger DA. Tuberous sclerosis complex diagnostic criteria update: recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. *Pediatr Neurol.* 2013;49: 243-254.
68. Aldrich CS, Hong CH, Groves L, Olsen C, Moss J, Darling TN. Acral lesions in tuberous sclerosis complex: insights into pathogenesis. *J Am Acad Dermatol.* 2010;63:244-251.
69. Webb DW, Clarke A, Fryer A, Osborne JP. The cutaneous features of tuberous sclerosis: a population study. *Br J Dermatol.* 1996;135:1-5.
70. Sparling JD, Hong CH, Brahim JS, Moss J, Darling TN. Oral findings in 58 adults with tuberous sclerosis complex. *J Am Acad Dermatol.* 2007;56:786-790.
71. Mlynarczyk G. Enamel pitting. A common sign of tuberous sclerosis. *Ann N Y Acad Sci.* 1991;615:67-69.
72. Robertson DM. Ophthalmic findings. In: Gomez MR, ed. *Tuberous Sclerosis Complex*. 3rd ed. New York, NY: Oxford University Press; 1999. p. 145-159.
73. Aronow ME, Nakagawa JA, Gupta A, Traboulsi EI, Singh AD. Tuberous sclerosis complex: genotype/phenotype correlation of retinal findings. *Ophthalmology.* 2012;119:1917-1923.
74. Krueger DA, Northrup H. Tuberous sclerosis complex surveillance and management: recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. *Pediatr Neurol.* 2013;49:255-265.
75. Bissler JJ, Kingswood JC, Radzikowska E, et al. Everolimus for angiomyolipoma associated with tuberous sclerosis complex or sporadic lymphangioleiomyomatosis (EXIST-2): a multicenter, randomised, double-blind, placebo-control trial. *Lancet.* 2013;381: 817-824.
76. Bissler JJ, McCormack FX, Young LR, et al. Sirolimus for angiomyolipoma in tuberous sclerosis complex or lymphangioleiomyomatosis. *N Engl J Med.* 2008;358:140-151.
77. McCormack FX, Inoue Y, Moss J, et al. Efficacy and safety of sirolimus in lymphangioleiomyomatosis. *N Engl J Med.* 2011;364: 1595-1606.
78. Franz DN, Belousova E, Sparangana S, et al. Efficacy and safety of everolimus for subependymal giant cell astrocytomas associated with tuberous sclerosis complex (EXIST-1): a multicenter, randomised, placebo-controlled phase 3 trial. *Lancet.* 2013;381:125-132.
79. Hofbauer GF, Marcollo-Pini A, Corsenca A, et al. The mTOR inhibitor rapamycin significantly improves facial angiofibroma lesions in a patient with tuberous sclerosis. *Br J Dermatol.* 2008;159:473-475.
80. Koenig MK, Hebert AA, Roberson J, et al. Topical rapamycin therapy to alleviate the cutaneous manifestations of tuberous sclerosis complex: a double-blind, randomized, controlled trial to evaluate the

safety and efficacy of topically applied rapamycin. *Drugs R D.* 2012;12:121-126.
81. Tanaka M, Wataya-Kaneda M, Nakamura A, Matsumoto S, Katayama I. First left-right comparative study of topical rapamycin vs. vehicle for facial angiofibromas in patients with tuberous sclerosis complex. *Br J Dermatol.* 2013;169:1314-1318.
82. Wataya-Kaneda M, Tanaka M, Nakamura A, Matsumoto S, Katayama I. A novel application of topical rapamycin formulation, an inhibitor of mTOR, for patients with hypomelanotic macules in tuberous sclerosis complex. *Arch Dermatol.* 2012;148:138-139.
83. Tu J, Foster RS, Bint LJ, Halbert AR. Topical rapamycin for angiofibromas in paediatric patients with tuberous sclerosis: follow up of a pilot study and promising future directions. *Australas J Dermatol.* 2014;55:63-69.
84. Orloff MS, He X, Peterson C, et al. Germline PIK3 CA and AKT1 mutations in Cowden and Cowden-like syndromes. *Am J Hum Genet.* 2013;92:76-80.
85. Bonneau D, Longy M. Mutations of the human PTEN gene. *Hum Mutat.* 2010;16:109-122.
86. Wang SI, Puc J, Li J, et al. Somatic mutations of *PTEN* in glioblastoma multiforme. *Cancer Res.* 1997;57:4183-4186.
87. Smith JS, Tachibana I, Passe SM, et al. P*TEN* mutation, *EGFR* amplification, and outcome in patients with anaplastic astrocytoma and glioblastoma multiforme. *J Natl Cancer Inst.* 2001;93:1246-1256.
88. Knobbe CB, Merlo A, Reifenberger G. Pten signaling in gliomas. *Neuro-Oncol.* 2002;4:196-211.
89. Groszer M, Erickson R, Scripture-Adams DD, et al. Negative regulation of neural stem/progenitor cell proliferation by the *PTEN* tumor suppressor gene in vivo. *Science.* 2001;294:2186-2189.
90. Pilarski P, Burt R, Kohlman W, Pho L, Shannon KM, Swisher E. Cowden Syndrome and the *PTEN* hamartoma tumor syndrome: systematic review and revised diagnostic criteria. *J Natl Cancer Inst.* 2013;105:1608-1616.
91. Tan MH, Mester J, Peterson C, et al. A clinical scoring system for selection of patients for PTEN mutation testing is proposed on the basis of a prospective study of 3042 probands. *Am J Hum Genet.* 2011;88:42-56.
92. Schaffer JV, Kamino H, Witkiewicz A, McNiff JM, Orlow SJ. Mucocutaneous neuromas. *Arch Dermatol.* 2006;142:625-632.
93. Farooq A, Walker LF, Bowling J, Audisio RA. Cowden syndrome. *Cancer Treat Rev.* 2010;36:577-583.
94. Wright K, Spiegel PH, eds. *Pediatric Opthalmology and Strabismus*. 2nd ed. New York, NY: Springer-Verlag; 2003.
95. Erkek E, Hizel S, Sanly C, et al. Clinical and histopathological findings in Bannayan-Riley-Ruvalcaba syndrome. *J Am Acad Dermatol.* 2005;53:639-643.
96. Tan MH, Mester JL, Ngeow J, Rybicki LA, Orloff MS, Eng C. Lifetime cancer risks in individuals with germline PTEN mutations. *Clin Cancer Res.* 2012;18:400-407.
97. Piccione M, Fragapane T, Antona V, Giachino D, Cupido F, Corsello G. PTEN hamartoma tumor syndromes in childhood: description of two cases and a proposal for follow-up protocol. *Am J Med Genet.* 2013;161A:2902-2908.
98. Schmid GL, Kassner F, Uhlig HH, et al. Sirolimus treatment of severe PTEN hamartoma tumor syndrome: case report and in vitro studies. *Pediatr Res.* 2014;75:527-534.
99. Iacobas I, Burrows PE, Adams DM, et al. Oral rapamycin in the treatment of patients with hamartoma syndromes and PTEN mutation. *Pediatr Blood Cancer.* 2011;57:321-323.
100. Enrolras O, Riche MC, Merland JJ. Facial port-wine stains and Sturge-Weber syndrome. *Pediatrics.* 1985;76:48-51.
101. Tallman B, Tan OT, Morelli JG, et al. Location of port-wine stains and the likelihood of ophthalmic and/or central nervous system complications. *Pediatrics.* 1991;87:323-327.
102. Garzon MC, Huang JT, Enjolras O, Frieden IJ. Vascular malformations. Part II: Associated syndromes. *J Am Acad Dermatol.* 2007;56: 541-564.
103. Khaier A, Nischal KK, Espinosa M, Manoj B. Periorcular port wine stain: the great Ormond street hospital experience. *Ophthalmology.* 2011;118:2274-2278.
104. Ch'ng S, Tan ST. Facial port-wine stains—clinical stratification and risks of neuro-ocular involvement. *J Plast Reconstr Aesthet Surg.* 2008;61:889-893.
105. Comi AM. Update on Sturge-Weber syndrome: diagnosis, treatment, quantitative measures, and controversies. *Lymphat Res Biol.* 2007;5: 257-264.
106. Piram M, Lorette G, Sirinelli D, Herbreteau D, Giraudeau B, Maruani A. Sturge-Weber syndrome in patients with facial port-wine stain. *Pediatr Dermatol.* 2012;29:32-37.
107. Shirley MD, Tang H, Gallione CJ, et al. Sturge-Weber syndrome and port-wine stains caused by somatic mutation in *GNAQ*. *N Engl J Med.* 2013;368:1971-1979.
108. Van Raamsdonk CD, Bezrookove V, Green G, et al. Frequent somatic mutations of GNAQ in uveal melanoma and blue naevi. *Nature.* 2009;457:599-602.
109. Shields CL, Kligman BE, Suriano M, et al. Phacomatosis pigmento-vascularis of cesioflammea type in 7 patients: combination of ocular pigmentation (melanocytosis or melanosis) and nevus flammeus with risk for melanoma. *Arch Ophthalmol.* 2011;129:746-750.
110. Anolik R, Newlove T, Weiss ET, et al. Investigation into optimal treatment intervals of facial port-wine stains using the pulsed dye laser. *J Am Acad Dermatol.* 2012;67:985-990.
111. Enjolras O, Riche MC, Merland JJ. Facial port-wine stains and Sturge-Weber syndrome. *Pediatrics.* 1985;76:48-51.
112. Sharan S, Swamy B, Taranath DA, et al. Port-wine vascular malformations and glaucoma risk in Sturge-Weber syndrome. *J AAPOS.* 2009;13:374-378.
113. Awad AH, Mullaney PB, Al-Mesfer S, Zwaan JT. Glaucoma in Sturge-Weber syndrome. *J AAPOS.* 1999;3:40-45.
114. Arora KS, Quigley HA, Comi AM, Miller RB, Jampel HD. Increased choroidal thickness in patients with Sturge-Weber syndrome. *JAMA Ophthalmol.* 2013;131:1216-1219.
115. Singh AD, Kaiser PK, Sears JE. Choroidal hemangiomas. *Ophthalmol Clin N Am.* 2005;18:151-161.
116. Shiau T, Armogan N, Yan DB, Thompson HG, Levin AV. The role of episcleral venous pressure in glaucoma associated with Sturge-Weber syndrome. *J AAPPOS.* 2012;16:61-64.
117. Kossoff EH, Buck C, Freeman JM. Outcomes of 32 hemispherectomies for Sturge-Weber syndrome worldwide. *Neurology.* 2002;59:1735-1738.
118. Lo W, Marchuk DA, Ball KL, et al. Updates and future horizons on the understanding, diagnosis, and treatment of Sturge-Weber syndrome brain involvement. *Dev Med Child Neurol.* 2012;54:214-223.
119. Sudarsanam A, Ardern-Holmes SL. Sturge-Weber syndrome: from the past to the present. *Eur J Paediatr Neurol.* 2014;18:257-266.
120. Lance EI, Sreenivasan AK, Zabel TA, Kossoff EH, Comi AM. Aspirin use in Sturge-Weber syndrome: side effects and clinical outcomes. *J Child Neurol.* 2013;28:213-218.
121. Bachur CD, Comi AM. Sturge-Weber syndrome. *Curr Treat Options Neurol.* 2013;15:607-617.
122. Kadonga JN, Frieden IJ. Neurocutaneous melanosis: definition and review of the literature. *J Am Acad Dermatol.* 1991;24:747-755.
123. Gerami P, Paller AS. Making a mountain out of a molehill: NRAS, mosaicism, and large congenital nevi. *J Invest Dermatol.* 2013;133: 2127-2130.
124. Kinsler VA, Thomas AC, Ishida M, et al. Multiple congenital melanocytic nevi and neurocutaneous melanosis are caused by postzygotic mutations in codon 61 of NRAS. *J Invest Dermatol.* 2013;133:2229-2236.
125. Bett BJ. Large or multiple congenital melanocytic nevi: occurrence of neurocutaneous melanocytosis in 1008 persons. *J Am Acad Dermatol.* 2006;54:767-777.
126. Marghoob AA, Dusza S, Olivieria S, Halpern AC. Number of satellite nevi as a correlate for neurocutaneous melanocytosis in patients with

large congenital melanocytic nevi. *Arch Dermatol.* 2004;140: 171-175.
127. Kiratli H, Sahin A. Fundus features of a case of neurocutaneous melanosis. *Ophthalmic Genet.* 2004;25:271-276.
128. Lam J, Dohil MA, Eichenfield LF, Cunningham BB. SCALP syndrome: sebaceous nevus syndrome, CNS malformations, aplasia cutis congenita, limbal dermoid, and pigmented nevus (giant congenital melanocytic nevus) with neurocutaneous melanosis: a distinct syndromic entity. *J Am Acad Dermatol.* 2008;58: 884-888.
129. Bekiesinska-Figatowska M, Szczygielski O, Boczar M, et al. Neurocutaneous melanosis in children with giant congenital nevi. *Clin Imaging.* 2014;38:79-84.
130. Ramaswamy V, Delaney H, Haque S, Marghoob A, Khakoo Y. Spectrum of central nervous system abnormalities in neurocutaneous melanosis. *Dev Med Child Neurol.* 2012;54:563-568.
131. Schaffer JV, McNiff NM, Bolognia JL. Cerebral mass due to neurocutaneous melanosis: eight years later. *Pediatr Dermatol.* 2001;18:369-377.
132. Kinsler VA, Chong WK, Aylett SE, Atherton DJ. Complications of congenital melanocytic naevi in children: analysis of 16 years' experience and clinical practice. *Br J Dermatol.* 2008;159:907-914.
133. Foster RD, Williams ML, Barkkovich AJ, et al. Giant congenital melanocytic nevi: the significance of neurocutaneous melanosis in neurologically asymptomatic children. *Plast Reconstr Surg.* 2001;107:9339-9341.
134. Price HN, Schaffer JV. Congenital melanocytic nevi-when to worry and how to treat: facts and controversies. *Clin Dermatol.* 2010;28:293-302.
135. Posch C, Moslehi H, Feeney L, et al. Combined targeting of MEK and PI3 K/mTOR effector pathways is necessary to effectively inhibit NRAS mutant melanoma *in vitro* and *in vivo*. *Proc Natl Acad Sci.* 2013;110:4015-4020.