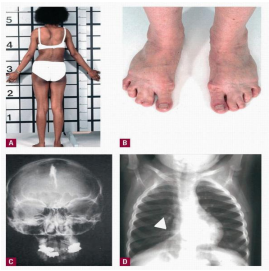

Basal Cell Nevus Syndrome

Basal cell nevus syndrome (BCNS), also known as nevoid basal cell carcinoma syndrome and Gorlin syndrome [Online Mendelian Inheritance in Man is a rare autosomal dominant disorder associated with a panoply of phenotypic abnormalities that can be divided into developmental anomalies and postnatal tumors, especially basal cell carcinomas (BCCs).[1] Although individual aspects had been reported previously, their syndromic association was first appreciated widely in the late 1950s.[2,3]

EPIDEMIOLOGY

The prevalence of BCNS is variously estimated to be 1 in 60,000 and 1 in 120,000 persons. The syndrome affects both sexes and occurs in a wide variety of cultural groups, and therefore does not have a predilection for a particular skin type. The condition appears to have complete penetrance and variable expressivity of traits, which makes clinical presentation among families variable. Further, as with many dominantly inherited conditions, new mutations are common. As a result, in many cases, patients may have no apparent affected ancestors or siblings.

ETIOLOGY AND PATHOGENESIS

Genetic Abnormality

All known BCNS patients thus far carry mutations in the PATCHED1 gene residing on the long arm of chromosome 9. PTCH1 plays a central role in the hedgehog signaling pathway that is essential for the establishment of normal body and limb patterning in metazoan organisms. The PTCH1 locus behaves like a classic tumor suppressor gene . The appearance of BCCs in small numbers at an older age in sporadic cases and in larger numbers at a younger age in patients with BCNS is reminiscent of differences in sporadic and hereditary cases of retinoblastoma. BCNS, like other tumor susceptibility syndromes, is inherited in an autosomal dominant manner, with inheritance of a loss-of-function allele followed by somatic loss of the remaining copy before tumor formation.

Identification of the gene mutation responsible for BCNS facilitated a molecular verification of the tumor suppressor prediction. In BCNS, patients inherit one defective PTCH1 allele, but their tumors contain an additional somatic mutation. As with other tumor suppressor genes, PTCH1 mutations have also been found in older adults with sporadic BCCs and other sporadic tumors known to be over-represented in BCNS patients (e.g., medulloblastomas and meningiomas), which supports the idea that two somatic “hits” are required in sporadic tumors.

PTCH1 Function

PTCH1 protein plays a critical role in the hedgehog signaling pathway. Genetic and biochemical studies in Drosophila and mammals indicate that PTCH1 protein inhibits this signaling pathway by inhibiting the function of the central G protein-coupled receptor smoothened (SMO), and that the extracellular ligand hedgehog reduces this inhibition. Signaling by SMO results in the activation of the GLI family of zinc finger proteins that mediate all the transcriptional effects of hedgehog signaling. Three GLI proteins mediate activation and suppression of hedgehog target genes, with GLI1 and GLI2 acting as activators and GLI2 and GLI3 as suppressors. SMO signaling tips the balance towards activation and away from target gene suppression. In mammals, GLI activity is controlled by the novel cytoplasmic protein Suppressor of Fused (SUFU), which promotes the transcriptional repression and inhibits activation.[16] SMO functions to inhibit SUFU activity, thus releasing GLI proteins to become transcriptional activators. When hedgehog binds to PTCH1, PTCH1 inhibition of SMO is relieved and the pathway is activated. The loss of PTCH1 function that allows unregulated SMO activity forms the basis of the tumor

induction.

How PTCH1 functions as a tumor suppressor is still under investigation. A significant aspect of PTCH1 function is inhibition of SMO, although how PTCH1 accomplishes this is unknown. PTCH1 acts in an enzymatic manner, with only a few molecules able to inhibit several-fold times more SMO.[17] Moreover, PTCH1 and SMO are thought not to physically interact and exist in distinct endosomes in the cell. One clue is that SMO activity appears to be linked to its sub-cellular location, because loss of PTCH1 or mutations that trap SMO at the membrane result in SMO phosphorylation and increased activity. [18] Another clue is that PTCH1 shares homology with sterolsensing domain-containing proteins such as the cleavage activation protein SREBP (sterol regulatory element-binding protein) and β-hydroxy-β-methylglutaryl-coenzyme A reductase.
[19]
It also shares significant structural identity with the resistance-nodulation-division (RND) permease family of small-molecule transporters, which suggests that it acts like a molecular pump. This evokes the tantalizing hypothesis that PTCH1 regulates SMO localization by regulating the production or distribution of small-molecule second messengers in the cell.

Mutations in Sonic Hedgehog Pathway in BCCs

Supporting the central role of Sonic Hedgehog (Shh) target gene induction in BCC pathogenesis is the finding of mutations in members of the Shh pathway in both BCNS patients and in sporadic BCCs. Identified mutations involving PTCH1 are by far the most common and are found in approximately 40 percent of tumors.[23] Epidemiologic evidence implicates ultraviolet light in the pathogenesis of sporadic BCCs. The particular type of mutation found in PTCH is consistent with mutation caused by ultraviolet light, which provides additional evidence for PTCH and sunlight in cancer development.

Mutations of SMO protein have been identified in approximately 10 percent of BCCs, and these mutations appear to render SMO protein resistant to PTCH1 inhibition.[25] Indeed, experimental transfection of cells with mutant SMO sequences can transform them to a malignant phenotype. This finding that BCCs may have upregulation of hedgehog target gene expression due to mutations in either PTCH1 or SMO argues that it is the upregulation of hedgehog signaling rather than the specific mutation that is crucial to BCC formation. Consistent with this is the finding that mutations in the gene encoding SUFU have been reported to underlie formation of medulloblastomas.

The identification of these molecular abnormalities in BCCs for the first time has permitted the development of mouse models of this tumor. Previously, insults to mouse skin—ultraviolet or ionizing radiation or carcinogenic chemicals—have produced papillomas and carcinomas of the squamous, but not the basal cell, lineage. Mouse models that show spontaneous development of BCC-like tumors include those with epidermal overexpression of hedgehog,[27] of mutant SMO,[25] or of GLI1[28,29] or GLI2.[30] In addition, ptc1[+/-] mice, which, like BCNS patients, have one instead of two functioning alleles of PTCH1, not only develop BCCs and related tumors but also develop plantar pits, medulloblastomas, and rhabdomyosarcomas, as do BCNS patients. The mouse BCCs (mimicking BCCs in BCNS patients) occur spontaneously in low numbers and in small sizes, but in much higher numbers and of larger size in mice exposed to ultraviolet or ionizing radiation.

CLINICAL FINDINGS

Cutaneous Lesions

Hedgehog signaling plays a critical role in the expansion of progenitor cells in a wide variety of tissues in both invertebrate and vertebrate organisms. PTCH1 normally is expressed both during development and in the adult, which suggests an ongoing role postnatally. Studies involving experimental models inappropriately expressing components of the hedgehog signaling pathway have revealed significant developmental anomalies.[31] The resemblance of these anomalies to those characteristic of BCNS implies that aberrant activation of the hedgehog signaling pathway is a sufficient explanation for the developmental and tumorigenic anomalies of BCNS, even if the precise pathogenic mechanisms have yet to be elucidated.

□ Frequency of Anomalies in Basal Cell Nevus Syndrome

□

□

IGR	**14**	**(FRANCE)**
EVANS ET AL. (UNITED KINGDOM)		
SHANLEY ET AL.	**5**	**(AUSTRALIA)**
KIMONIS ET AL.	**13**	**(USA)**

Number of cases

22

84

118

105

Number of families

5

29

64

26

Average age (yr)

44.9

35

34.5

Sex ratio (Male:Female)

1:1.75

1:1.3

1:1.3

1:1.2

BCC (%)

100

47

76

80

Average age at first BCC (yr)

24.2

20.3

21.4

Palmar pits (%)

45

71

80

8

Dental cysts (%)

62

66

75

74

Falx calcification (%)

66

92

65

Epidermal cysts (%)

41

51

Craniofacial Anomalies

Macrocephaly (%)

27

80

49

Skull protrusion (%)

18

66

26

Cleft palate (%)

?

5

4

3

Ophthalmologic Anomalies

Hypertelorism (%)

18

6

42

Strabismus (%)

4.5

19

Skeletal Anomalies

Pectus excavatum (%)

23

23

12

Scoliosis (%)

18

31

Kyphosis (%)

9

Cervical ribs (%)

5

16

Bifid ribs (%)

16

26

Spina bifida (%)

9

19

Vertebral fusion (%)

4.5

10

Neurologic Anomalies

Anosmia (%)

4.5

9

Deafness (%)

4.5

Corpus collosum tumor (%)

9

10

Tumors

Medulloblastoma (%)

13

4

1

4

Meningioma (%)

18

1

5

Ovarian fibroma (%)

13

24

14

17

BCC = basal cell carcinoma; IGR = intrauterine growth retardation.

From Pruvost-Balland C, *Ann Dermatol Venereol* **133** (2006) 117–121, with permission. Recherche de mutations germinales du gène PTCH1 dan

Patients with BCNS show multiple abnormalities, none of which is unique to this syndrome. The three abnormalities considered to be most characteristic of the syndrome are tumors such as medulloblastomas or BCCs, pits of the palms and soles, and odontogenic cysts of the jaw.

BCCs in patients with BCNS cannot be distinguished individually from those in sporadic cases , which is not surprising in view of the similar pathogenesis in familial and sporadic cases. What

is distinguishing is their appearance in large numbers starting at an early age. They may be banal appearing and confused grossly with nevocytic nevi—hence the name basal cell nevus. They may also have a translucent, papulonodular appearance more characteristic of sporadic basal cell carcinomas and may invade locally. In rare cases, they may even metastasize, causing the patient's death. Although the ratio of sun-protected to sun-exposed BCCs may be higher in BCNS than in sporadic cases, sunlight and ionizing radiation clearly accelerate BCC formation in BCNS patients, and darkly pigmented BCNS patients may have few to no BCCs .Palmo-plantar pits are small defects in the stratum corneum and may be pink or, if dirt has accumulated, dark in color . They appear early in life and can be a valuable aid in diagnosis in addition to jaw cysts or medulloblastoma. Their basis is poorly understood, but they are thought to be due to aborted attempts to generate hair follicles in the palms. They are also seen in mouse PTCH1 heterozygotes.

Related Physical Findings

Tissue overgrowth, which is also a feature of hedgehog signaling pathway activation in Drosophila, often is manifested by an overall body size larger than that of other family members. Limbs may be particularly long, giving a marfanoid appearance , and a large head circumference (at least in probands) and frontal bossing are often described.

Jaw cysts often are the first detectable abnormality. They may be asymptomatic and therefore diagnosed only radiologically. However, they also may erode enough bone to cause pain, swelling, and loss of teeth. They occur more often in the mandibular jaw than in the maxillary jaw. They presumably form from inappropriate Shh induction of dental epithelium, can recur often, and can be the most debilitating aspect of the syndrome.

. These include tissue overgrowth seen in other epithelial organs such as the meninges or ovary that give rise to meningiomas or ovarian fibromas. Variation in clinical severity is typical even within a single kindred, and this heterogeneity is likely due to both environmental differences (e.g., exposure to ultraviolet and ionizing radiation) and genetic background differences.

Of interest is the finding that Shh signaling plays a key role in up to 25 percent of all human cancers, including small cell lung cancer, pancreatic cancer, and prostate cancer.[34] This finding suggests a wider role for hedgehog signaling than that seen in BCNS patients. Although BCNS is a rare syndrome and exhaustive controlled studies have not been performed, no excess of these associated cancers has been documented in BCNS patients. This might reflect a distinct

mechanism of action, because these other tumors demonstrate hedgehog ligand overexpression rather than the loss of PTCH1. Alternatively, pathway induction in older adults may have different consequences than pathway activation in younger individuals.

□ DIAGNOSIS

Because the individual abnormalities are not unique to BCNS patients, it is possible to diagnose BCNS clinically only when multiple typical defects are present . The severity of abnormalities may differ markedly among members of a single kindred, and diagnostic certainty may be difficult for specific individuals even if they belong

to a kindred with known BCNS. Generally, the diagnosis is suggested to the dermatologist when multiple BCCs arise in a patient at an unexpectedly early age and in unexpectedly large numbers, with the average age of onset in the early 20s.

Further evaluation should include (1) questions about whether other family members have had abnormalities consistent with BCNS (although perhaps 25 percent to 30 percent of patients with BCNS have no affected ancestors) and whether the patient is taller and heavier than his or her relatives; (2) examination for palmo-plantar pits and skin cysts and assessment of body and head size; and (3) radiologic evaluation for jaw cysts (which often appear around the start of the second decade and frequently recur after surgery), calcification of the falx (which occurs in nearly all adults with BCNS and may be present in early childhood in BCNS patients, thus suggesting the diagnosis of BCNS in patients with early-onset medulloblastomas), and abnormalities of the ribs, spine, and phalanges (flame-shaped lucencies), each of which is present in one-third to one-half of BCNS patients. Kimonis and colleagues proposed a set of major and minor criteria for presumptive diagnosis of BCNS, which has since been modified . For cases in which the diagnosis is in doubt, or for genotyping of other family members, identification of PTCH1 gene mutations is now available commercially through GeneDX (Gaithersburg, MD).

□ DIFFERENTIAL DIAGNOSIS

Other syndromes exist that are characterized by the development of multiple BCCs. These include Bazex syndrome Rombo syndrome and a syndrome observed in a family with BCCs, milia, and coarse, sparse hair. Hair abnormalities are present in all three syndromes, which is a finding of interest in view of the often-repeated suggestion that BCCs arise from hair follicles rather than from interfollicular epidermis. The exact nosologic relationships among these three syndromes are uncertain, but patients with BCNS have normal hair, and all three syndromes seem quite different from BCNS.

Two other syndromes that have been described include multiple hereditary infundibulocystic basal cell carcinoma[40] and generalized basaloid follicular hamartoma. Both demonstrate histologic variants of BCCs, with more hamartomatous lesions, and are characterized by palmar pits and milia. The latter syndrome is acquired and associated with autoimmune disease, which suggests an immunologic stimulation of the hedgehog pathway. The former appears to be linked to the PTCH1 locus and thus may be due to a PTCH1 allele.

Patients with long-term arsenic ingestion may have multiple BCCs. Their dyschromia and lack of other phenotypic abnormalities differentiate them from BCNS patients . Patients with xeroderma pigmentosum develop multiple BCCs but are readily differentiated from BCNS patients by their severe photosensitivity and other phenotypic abnormalities .

The most challenging patients are those who have a marked propensity to develop multiple BCCs early in life, sometimes sporadically or in rare cases after therapeutic irradiation (e.g., for Hodgkin disease) without showing any of the other signs of BCNS. These cases occasionally produce diagnostic confusion because, due to the variable expressivity of individual PTCH1 alleles, it is not known whether their defect is related to the hedgehog pathway, to DNA repair, to an unknown toxin, and/or to undescribed mechanisms. One insightful study argues against constitutional PTCH1 mutations as the cause of multiple BCCs, because PTCH1 mutations have not been found in individuals who do not have at least one other key manifestation of BCNS.

COMPLICATIONS, PROGNOSIS, AND CLINICAL COURSE

Although disease pathogenesis involves abnormalities in Shh signaling, the wide variability in clinical course among families,

and even between generations of the same family, make prediction of clinical course difficult. If BCNS is suspected or confirmed, physicians should also screen for the most frequent sequelae of the disease during childhood or adolescence.. No large-scale survival studies have been performed to determine whether BCNS patients die earlier because of their disease.[13],[43] The major complications are associated with developmental abnormalities that result in developmental delay or physical impairment in children and the childhood tumors that arise, such as medulloblastoma. The latter often occur within the first 5 years of life and are frequently the initial sign of BCNS. Complications arising from medulloblastoma treatment (radiation, shunt placement) are relatively common, and multidisciplinary teams of physicians are required to optimally treat these patients.

In the skin, BCCs that arise are locally aggressive but very rarely metastasize. No reports document an increased risk for metastatic BCCs, which suggests that the basic character of the tumor is similar to that seen in sporadic BCC cases. However, because of the high numbers and wide distribution of the tumor, even in the absence of sun exposure, involvement of key epithelial surfaces or membranes is likely and can be disfiguring for the patient.

 TREATMENT

Therapy must be directed at the individual lesions as they arise, and the most important aspect of management is frequent examination, enthusiastic counseling about avoidance of sun exposure, and early treatment of small tumors. In animal models of BCNS, small clinically undetectable tumors arise throughout the skin. This suggests that many more tumors form than are detectable visibly by the clinician. This has several therapeutic ramifications. One is that clinicians caring for BCNS patients should become confident in their clinical acumen so that they can diagnose and treat tiny BCCs without histopathologic confirmation. This would eliminate multiple scar-inducing biopsies in addition to potentially disfiguring treatments. Another is that invasive treatments should be focused on those lesions that are potentially most harmful, such as those invading mucous membrane or adjacent structures. Repetitive surgical treatments run the risk of severe disfigurement for the patient. Finally, clear surgical margins may be difficult to achieve when using Mohs surgery, so aggressive pursuit of a clear margin needs to be balanced against other factors in treating these patients.

Diagnostic Criteria for Basal Cell Nevus Syndrome (BCNS)

Non-surgical approaches to BCC treatment should be used aggressively in BCNS patients when possible. Because the key is to convince the patient to accept frequent treatments, minimization of discomfort and scarring is a major goal. Approaches that may be of benefit are topical treatment with 5-fluorouracil (with or without occlusion, depending on the degree of inflammation produced), the Toll-like receptor agonist imiquimod, and photodynamic therapy. Oral therapy with retinoids also may be of value, but often only at a dosage that causes severe side effects.

Studies have now identified a natural antagonist of the hedgehog pathway derived from the Veratrum californicum

plant called cyclopamine. This substance binds and antagonizes SMO activity and has been shown to be effective in animal models of BCCs. Other small-molecule hedgehog pathway antagonists with similar properties have been identified and are currently being tested for their clinical efficacy. These bring the promise of a specific therapy for BCCs and other hedgehog signaling-dependent tumors. The x-irradiation of BCCs has been advocated in otherwise normal patients who are not surgical candidates. However, excessive radiation should be avoided if possible, because enhanced radiation-induced carcinogenesis (e.g., in the skin of the portals of irradiation for childhood medulloblastomas) is characteristic of BCNS. Patients with BCNS who receive radiation have developed an unusually large number of basal cell tumors in the irradiated area a short time after exposure . Radiosensitivity in PTCH heterozygotes has also been detected at the cellular level, although the mechanism is poorly understood.

Genetic counseling is appropriate. With the availability of direct sequencing of the PTCH1 locus,

genotyping for prenatal diagnosis is potentially achievable for interested families. Because PTCH1 is transmitted with complete penetrance, half of the children of affected individuals are expected to develop BCNS.