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Nevoid Basal Cell Carcinoma Syndrome

Synonyms: Basal Cell Nevus Syndrome (BCNS), Gorlin Syndrome, NBCCS

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Summary

Clinical characteristics

Nevoid basal cell carcinoma syndrome (NBCCS) is characterized by the development of multiple jaw keratocysts, frequently beginning in the second decade of life, and/or basal cell carcinomas (BCCs) usually from the third decade onward. Approximately 60% of individuals have a recognizable appearance with macrocephaly, frontal bossing, coarse facial features, and facial milia. Most individuals have skeletal anomalies (e.g., bifid ribs, wedge-shaped vertebrae). Ectopic calcification, particularly in the falx, is present in more than 90% of affected individuals by age 20 years. Cardiac and ovarian fibromas occur in approximately 2% and 20% of individuals respectively. Approximately 5% of all children with NBCCS develop medulloblastoma (primitive neuroectodermal tumor), generally the desmoplastic subtype. The risk of developing medulloblastoma is substantially higher in individuals with an *SUFU* pathogenic variant (33%) than in those with a *PTCH1* pathogenic variant (<2%). Peak incidence is at age one to two years. Life expectancy in NBCCS is not significantly different from average.

Diagnosis/testing

The diagnosis of NBCCS is established in a proband who fulfills existing diagnostic clinical criteria. Identification of a heterozygous germline pathogenic variant in *PTCH1* or *SUFU* on molecular genetic testing establishes the diagnosis if clinical features are inconclusive.

Management

Treatment of manifestations: Best provided by specialists experienced with the condition; keratocysts usually require surgical excision; early treatment of BCCs to ensure complete eradication of aggressive BCCs and to preserve normal tissue to prevent disfigurement; sonic hedgehog inhibitors such as vismodegib to treat severe BCCs; preservation of ovarian tissue whenever ovarian fibromas require surgical treatment. However, the cost of

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treatment has meant that the National Institute for Health and Care Excellence in the UK has judged the treatment not cost effective.

Prevention of primary manifestations: Avoidance of direct sun exposure through the use of complete sunblock and covering of exposed skin with long sleeves, high collars, and hats.

Surveillance: Monitoring of head circumference throughout childhood; developmental assessment and physical examination every six months in the first years of life because of increased risk for medulloblastoma; in those older than age eight years, orthopantogram every 12-18 months to identify jaw keratocysts; skin examination at least annually.

Agents/circumstances to avoid: Radiotherapy if there are alternative treatments, especially in childhood; diagnostic x-rays should be used sparingly; direct sun exposure should be limited; excessive sun exposure increases the likelihood of developing BCCs.

Evaluation of relatives at risk: Because of the need for surveillance for complications of NBCCS (medulloblastoma in children; jaw cysts and BCCs in adults) and the need to avoid sun exposure, clarification of the genetic status of at-risk relatives, including children, is appropriate.

Genetic counseling

NBCCS is inherited in an autosomal dominant manner. Approximately 70%-80% of individuals with NBCCS have an affected parent and about 20%-30% have NBCCS as the result of a *de novo* pathogenic variant. The offspring of an affected individual are at a 50% risk of inheriting NBCCS. Prenatal testing for pregnancies at risk is possible if the *PTCH1* or *SUFU* pathogenic variant has been identified in an affected family member.

Diagnosis

Suggestive Findings

Nevoid basal cell carcinoma syndrome (NBCCS) **should be suspected** in individuals with the following findings, which constitute major or minor diagnostic criteria.

Major criteria

- **Lamellar (sheet-like) calcification of the falx** or clear evidence of calcification in an individual younger than age 20 years. Falx calcification is nearly always present and is visible on anteroposterior (AP) x-rays of the skull after age 20 years (see **Notes regarding radiographs**).
- **Jaw keratocyst.** Odontogenic keratocyst histologically; seen on orthopantogram as an area of translucency
- **Palmar/plantar pits** (≥2); particularly useful in diagnosis and more pronounced when the hands and feet are soaked in warm water for up to ten minutes. Pits may appear as white "punched-out" or pink "pin-prick" lesions.
- **Multiple basal cell carcinomas (BCCs)** (>5 in a lifetime) or a BCC before age 30 years. Provision needs to be made for decreased risk of BCC in individuals with dark skin and increased risk in those with light skin living in hot sunny climates, particularly those with type 1 Celtic skin and red hair, and of this group, particularly those with the common *MC1R* variant (rs1805007), which can modify age of onset for NBCCS [Yasar et al 2015].
- **First-degree relative with NBCCS**

Minor criteria

- Childhood medulloblastoma (also called primitive neuroectodermal tumor)

Note: A consensus meeting consisting of US-based experts (with one French participant) has suggested changing medulloblastoma to a major criterion and allowing the diagnosis of NBCCS with only two minor criteria in addition to a major criterion [Bree et al 2011]. The concern would be that this would reduce the specificity of diagnostic criteria, as individuals with medulloblastoma undergoing radiotherapy without NBCCS are likely to develop more than one BCC. Confining the medulloblastoma diagnosis to nodular/desmoplastic and disallowing BCCs occurring after radiotherapy as a major criterion may improve sensitivity without losing specificity. These changes have not yet been adopted. A consensus conference on screening recommendations convened by the American Association of Cancer Research did not propose adopting the Bree et al criteria [Foulkes et al 2017].

- Lympho-mesenteric or pleural cysts
- Macrocephaly (OFC >97th centile)
- Cleft lip/palate
- Vertebral/rib anomalies observed on chest x-ray and/or spinal x-ray (see **Notes regarding radiographs**): bifid/splayed/extra ribs; bifid vertebrae
- Preaxial or postaxial polydactyly
- Ovarian/cardiac fibromas
- Ocular anomalies (e.g., cataract, developmental defects, and pigmentary changes of the retinal epithelium)

Notes regarding radiographs

- To verify a clinical diagnosis of NBCCS, AP and lateral x-rays of the skull, an orthopantogram, chest x-ray, and spinal x-ray are usually necessary.
- Clinicians should avoid using x-rays in childhood if the diagnosis is obvious without them or if a known pathogenic variant exists in the family.
- If radiographs have already been taken (i.e., before the diagnosis of NBCCS is being considered) it is preferable to obtain and review the original radiographs rather than repeat them because individuals with NBCCS are susceptible to x-irradiation.
- Even when present, bifid ribs, bifid vertebrae, and falx calcification are often not mentioned in formal reports of radiographic findings, as these can also be normal variations in the general population.
- X-ray findings may be helpful in suggesting or confirming the diagnosis in young children with cardiac fibromas, cleft lip/palate, polydactyly, or macrocephaly [Debeer & Devriendt 2005, Veenstra-Knol et al 2005].

Establishing the Diagnosis

The diagnosis of NBCCS **is established** in a proband with the following findings:

- Two major diagnostic criteria and one minor diagnostic criterion or one major and three minor diagnostic criteria [Evans et al 1993]. A similar series of diagnostic criteria was proposed by Kimonis et al [1997]. No study has been able to assess which combination of diagnostic criteria represents the best trade-off between sensitivity and specificity.
- Identification of a heterozygous germline *PTCH1* or *SUFU* pathogenic variant on molecular genetic testing (see Table 1). This finding establishes the diagnosis if clinical features are inconclusive.

  Note: (1) Occasional variants in *PTCH2* have been found in individuals with NBCCS but these may not be conclusive [Fujii et al 2013]. Likewise, *SUFU* pathogenic variants may not always cause typical NBCCS

(see Genetically Related Disorders). (2) Identification of an identical *PTCH1* pathogenic variant in two or more separate tumors but not present (or present at a lower-than-normal ratio) in lymphocyte DNA confirms the presence of mosaicism [Evans et al 2007].

Molecular testing approaches can include **serial single-gene testing**, use of a **multigene panel**, and **more comprehensive genomic testing**.

Serial single-gene testing. Suggested order:

1. Sequence analysis of *PTCH1*
2. Gene-targeted deletion/duplication analysis of *PTCH1*
3. Sequence analysis of *SUFU*
4. Gene-targeted deletion/duplication analysis of *SUFU*
5. RNA analysis of *PTCH1*

Note: *SUFU* molecular testing should be considered first in families with medulloblastoma and without jaw keratocysts [Smith et al 2014].

A multigene panel that includes *PTCH1, SUFU* and other genes of interest (see Differential Diagnosis) may also be considered. Note: (1) If only NBCCS is being considered, a bespoke panel of just *PTCH1* and *SUFU* should be considered optimal as large multigene panels may have decreased sensitivity and may not include gene-targeted deletion/duplication analysis or *PTCH1* RNA analysis necessary to identify large rearrangements [Smith et a 2014, Smith et al 2016]. (2) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (3) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*; thus, clinicians need to determine which multigene panel is mot likely to identify the genetic cause of condition at the most reasonable cost while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

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

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

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

Table 1. Molecular Genetic Testing Used in Nevoid Basal Cell Carcinoma Syndrome

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
PTCH1	Sequence analysis [3, 4]	50%-85% [4, 5]
	Gene-targeted deletion/duplication analysis [6]	6%-21% [7]
SUFU	Sequence analysis [3]	5% [8]
	Gene-targeted deletion/duplication analysis [6]	~1% [8]

Table 1. continued from previous page.

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
Unknown	NA	15%-27% [9]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Pathogenic variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Sequence analysis that detects deep intronic variants may be appropriate. Rare deep intronic variants that alter splicing are predicted to cause loss of function of protein patched homolog 1 [Bholah et al 2014].
5. Sequence analysis of exons 2-23 with intron-exon junctions and one of the splice forms of exon 1 of transcript variant NM_000264.4 detects pathogenic variants in 50%-85% of individuals with typical clinical findings of NBCCS. Individuals and families with no other features apart from multiple BCCs have a very small probability of having a *PTCH1* pathogenic variant [Klein et al 2005, Marsh et al 2005, Evans et al 2017].
6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
7. Eight of 38 individuals with NBCCS had large deletions that were not identified using sequence analysis [Nagao et al 2011].
8. Smith et al [2014]
9. Smith et al [2014], Evans et al [2017]

Clinical Characteristics

Clinical Description

More than 100 features that are variable within and among families have been associated with nevoid basal cell carcinoma syndrome (NBCCS) [Farndon 2004]. Findings are presented here in the usual order of manifestation.

Macrocephaly. The first feature likely to be observed is relative macrocephaly. A large proportion of babies with NBCCS require delivery by cesarean section because of large head size. After birth, the head growth pattern often resembles that of arrested hydrocephalus, but hydrocephaly requiring treatment is rare. Head circumference increases above the 97th centile until age ten to 18 months and then maintains its centile.

Other congenital malformations, found in approximately 5%, include cleft lip/palate (5%), polydactyly, and severe eye anomalies. Eye findings include strabismus, cataract, orbital cyst, microphthalmia, and pigmentary changes of the retinal epithelium [Black et al 2003, Ragge et al 2005].

Gross motor delay. There is often some delay in motor milestones; most individuals catch up by about age five years. No published psychometric evidence for global delay exists.

Medulloblastoma. Approximately 5% of all individuals with NBCCS develop the childhood brain malignancy medulloblastoma (now often called primitive neuroectodermal tumor) [Cowan et al 1997]. The tumor tends to be of desmoplastic histology [Amlashi et al 2003] and to have a favorable prognosis. Peak incidence of medulloblastoma in NBCCS is at approximately age one to two years, compared to age seven years in its sporadic form [Cowan et al 1997, Amlashi et al 2003].

More recently, nonsense and missense variants and multiexon deletion of *SUFU* were identified in three families with classic NBCCS features; one individual in each family had medulloblastoma [Smith et al 2014]. *SUFU*-related NBCCS is associated with a high risk for medulloblastoma of up to 33% (3/9) and a high meningioma risk post radiation. The risk for medulloblastoma in *PTCH1*-related NBCCS was less than 2% [Smith et al 2014].

Facies. Approximately 60% of individuals with a *PTCH1* pathogenic variant have a recognizable appearance with frontal bossing, coarse facial features, and facial milia. Facial features are likely more subtle in individuals with an *SUFU* pathogenic variant.

Skeletal features. Congenital bone anomalies are present at birth but will not be evident clinically in a newborn. The shoulders slope downward. Most individuals have skeletal anomalies identified on radiographs (e.g., bifid ribs, wedge-shaped vertebrae). Severe skeletal defects resulting from multiple rib/vertebral anomalies have been reported but are uncommon, as is open spina bifida.

Ectopic calcification, particularly in the falx, is present in more than 90% of individuals by age 20 years [Ratcliffe et al 1995, Kimonis et al 2004]. Sella calcification, when present, is visible on lateral x-rays of the skull.

Jaw keratocysts. Approximately 90% of individuals with *PTCH1*-related NBCCS develop multiple jaw keratocysts. They can occur as early as age five years, but the peak occurrence is in the teenage years. Jaw keratocysts usually present as painless swellings. Untreated, they can lead to major tooth disruption and fracture of the jaw. Jaw cysts rarely occur after age 30 years.

Jaw cysts have not been reported in individuals with *SUFU*-related NBCCS [Smith et al 2014].

A rare malignant transformation of a keratocyst called ameloblastoma has been reported in individuals with NBCCS at least six times [Ponti et al 2012].

Basal cell carcinomas (BCCs). Brownish/pink/orange basal cell nevi may occur in early childhood and may lie quiescent without evidence of aggressive behavior. The histologic appearance is that of a typical BCC which, when excised, can be the first, unexpected finding of NBCCS in simplex cases (i.e., affected individuals with no known family history of NBCCS), especially children. Active BCCs may grow from existing basal cell nevi that may be numerous, or typical BCCs may appear from virtually blemish-free skin. BCCs may also crust, bleed, and ulcerate, or may present as a localized infection.

BCCs can occur in early childhood, but in general do not present until the late teens or early adulthood. They occur more frequently with age, although 10% of individuals with NBCCS never develop a BCC. Individuals with type 1 skin (white skin that burns, but never tans, e.g., Celtic skin) and individuals with excessive ultraviolet light exposure seem especially prone to developing large numbers of BCCs. Clinically some affected individuals appear to be particularly radiosensitive, with new BCCs appearing in the field of radiation following radiotherapy.

Other skin manifestations include meibomian cysts in the eyelids, sebaceous cysts, and dermoid cysts. Skin tags (especially around the neck) often have the histologic appearance of BCCs but do not act aggressively.

Other tumors. Cardiac and ovarian fibromas occur, respectively, in approximately 2% and 20% of females [Evans et al 1993, Gorlin 2004]. Cardiac fibromas are usually present at birth or soon after. They can be asymptomatic or can cause arrhythmia or obstruction of cardiac flow. Rhabdomyomas may occur at other sites as well as in the heart [Watson et al 2004].

Ovarian fibromas occur with both *SUFU* and *PTCH1*-related NBCCS and may be more common in individuals with *SUFU*-related NBCCS [Evans et al 2017]. They are usually an incidental finding on ultrasound examination or at cesarean section. They may cause torsion of the ovary, but are not thought to affect fertility. They can become large and calcified; however, malignant transformation is uncommon.

The risk for other malignant tumors is not clearly increased, although lymphoma [Pereira et al 2011] and meningioma have been reported [Kijima et al 2012].

Morbidity/mortality. Life expectancy in NBCCS is not significantly different from average [Wilding et al 2012]. The major problem is with the cosmetic effect of treatment of multiple skin tumors and usually, to a lesser extent,

treatment of jaw keratocysts. A poor cosmetic outcome can lead to social difficulties, including difficulty maintaining employment.

Phenotype Correlations by Gene

PTCH1

A recent review of 182 genotyped individuals with NBCCS found that individuals with *PTCH1*-related NBCCS were more likely to be diagnosed earlier (p=0.02), have jaw cysts (p=0.002), and have bifid ribs (p=0.003) or any skeletal abnormality (p=0.003), than individuals with no identified pathogenic variant [Evans et al 2017].

Approximately 90% of individuals with *PTCH1*-related NBCCS develop multiple jaw keratocysts.

Approximately 60% of individuals with a *PTCH1* pathogenic variant have a recognizable appearance with frontal bossing, coarse facial features, and facial milia.

The risk for medulloblastoma in *PTCH1*-related NBCCS was lower than 2% [Smith et al 2014].

SUFU

SUFU-related NBCCS is associated with a high risk for medulloblastoma of up to 33% (3/9) and a high meningioma risk post radiation.

Facial features are likely more subtle in individuals with an *SUFU* pathogenic variant.

Overall, clinical features are milder in individuals with *SUFU*-related NBCCS with less BCCs, and no jaw cysts reported [Evans et al 2017].

Genotype-Phenotype Correlations

PTCH1. Individuals with *PTCH1* missense variants were diagnosed later (p=0.03) and were less likely to develop ten or more BCCs and jaw cysts than those with other *PTCH1* pathogenic variants (p=0.03).

Penetrance

Although NBCCS shows intra- and interfamilial variation in expression, experience clinically and from molecular testing is compatible with complete penetrance [Author, personal observation]. A previous report of reduced penetrance in a family with medulloblastoma based on *PTCH1* linkage analysis was refuted when the family was shown to have an *SUFU* pathogenic variant. [Smith et al 2014]. The penetrance of *SUFU* pathogenic variants is more difficult to determine, but is likely to be reduced.

Prevalence

Few studies of NBCCS prevalence exist. The most quoted prevalence figure, 1:57,000, comes from a study of a UK population of four million in northwest England [Evans et al 1991b]. Since publication of the study, an increased awareness of NBCCS and consequent increased diagnosis has led to a revision of that figure to nearer to 1:30,827 [Evans et al 2010]. The true figure may be even higher, as individuals with milder features may not be recognized.

A study in Australia gave a minimum prevalence of 1:164,000 [Shanley et al 1994].

Birth incidence has been confirmed to be as high as1:18,976 [Evans et al 2010].

Genetically Related (Allelic) Disorders

PTCH1

Ming et al [2002] reported heterozygous *PTCH1* pathogenic missense variants in five of 100 unrelated probands with holoprosencephaly. The authors hypothesized that the pathogenic missense variants would lead to enhanced repressive activity of *PTCH1* on the hedgehog signaling pathway, unlike the mechanism in NBCCS in which the pathway is activated, usually by haploinsufficiency for protein patched homolog 1 encoded by *PTCH1*. Ribeiro et al [2006] reported four further *PTCH1* pathogenic missense variants associated with holoprosencephaly.

A non-recurrent deletion (i.e., a deletion with many different possible breakpoints and many different sizes) at chromosome 9q22.3 encompassing a 352-kb critical region including *PTCH1* is characterized by the clinical findings of NBCCS as well as developmental delay and/or intellectual disability, metopic craniosynostosis, obstructive hydrocephalus, pre- and postnatal macrosomia, and seizures. Affected individuals are also at increased risk for Wilms tumor. The clinical spectrum of the 9q22.3 deletion is variable and the clinical findings depend somewhat on the size of the microdeletion. The 9q22.3 microdeletion cannot be identified by routine analysis of G-banded chromosomes or other conventional cytogenetic banding techniques, except with extremely large deletions [Muller et al 2012].

SUFU

Heterozygous germline truncating *SUFU* pathogenic variants were identified in two families that included several children with medulloblastoma. None of the family members with the *SUFU* pathogenic variant had clinical features of NBCCS [Brugières et al 2010]. Seventeen individuals with medulloblastoma and germline *SUFU* pathogenic variants reported by Guerrini-Rousseau et al [2018] did not meet NBCCS diagnostic criteria.

Differential Diagnosis

The differential diagnosis depends on the mode of presentation.

Macrocephaly

If the proband is a baby with macrocephaly and other birth defects, a limited number of overgrowth syndromes including Sotos syndrome and Beckwith-Wiedemann syndrome need to be considered.

Sotos syndrome is characterized by three cardinal clinical features: a distinctive facial appearance, learning disability, and overgrowth (increased height and head circumference ≥2 SD above the mean). Major features of Sotos syndrome include behavioral problems, advanced bone age, cardiac anomalies, cranial MRI/CT abnormalities, joint hyperlaxity/pes planus, maternal preeclampsia, neonatal jaundice, neonatal hypotonia, renal anomalies, scoliosis, and seizures. The risk for sacrococcygeal teratoma and neuroblastoma is slightly increased. The diagnosis is established in a proband by identification of a heterozygous *NSD1* pathogenic variant. Sotos syndrome is inherited in an autosomal dominant manner with more than 95% of individuals having a *de novo* pathogenic variant.

Beckwith-Wiedemann syndrome (BWS) is a disorder of growth variably characterized by neonatal hypoglycemia, macrosomia (large body size), macroglossia, hemihyperplasia, omphalocele, embryonal tumors (e.g., Wilms tumor, hepatoblastoma, neuroblastoma, rhabdomyosarcoma), visceromegaly, adrenocortical cytomegaly, renal abnormalities (e.g., medullary dysplasia, nephrocalcinosis, medullary sponge kidney, nephromegaly), and ear creases/pits. Macroglossia and macrosomia are generally present at birth but may have postnatal onset. Growth rate slows around age seven to eight years. Hemihyperplasia may affect segmental

regions of the body or selected organs and tissues. A provisional diagnosis of BWS based on clinical assessment may be confirmed by molecular/cytogenetic testing. BWS is associated with abnormal regulation of gene transcription in two imprinted domains on chromosome 11p15.5.

Isolated hydrocephaly or **megalencephaly** may be distinguished by clinical examination, family history, and x-rays.

Basal Cell Carcinomas (BCCs)

If the initial presentation is multiple BCCs, clinical examination and radiographs should nearly always establish the diagnosis of NBCCS.

Other inherited disorders with similar skin findings include the following:

- Brooke-Spiegler syndrome, characterized by trichoepitheliomas, milia, and cylindromas. Brooke-Spiegler syndrome presents in the second or third decade. It is caused by pathogenic variants in *CYLD* and inherited in an autosomal dominant manner. The milia are miniature trichoepitheliomas and appear only in sun-exposed areas.
- Bazex syndrome, characterized by multiple BCCs, follicular atrophoderma on the dorsum of hands and feet, decreased sweating, and hypotrichosis (OMIM 301845). The pitting on the backs of the hands is reminiscent of orange peel and quite unlike the palmar and plantar pits of NBCCS. The inheritance pattern is either autosomal dominant or X-linked.
- Rombo syndrome, a dominantly inherited condition similar to Bazex syndrome, reported in a single family (OMIM 180730). Skin findings are vermiculate atrophoderma, milia, hypotrichosis, trichoepitheliomas, BCCs, and peripheral vasodilation with cyanosis. The skin is normal until later childhood; BCCs develop in adulthood. Sweating is normal.
- An autosomal dominant or X-linked syndrome of hypotrichosis and BCCs, reported in a single family [Oley et al 1992] (OMIM 301845)
- Autosomal dominant inheritance of multiple basal cell carcinomas in the absence of other features

Acquired causes of multiple BCCs include arsenic exposure.

Jaw Keratocysts

If the initial presentation is jaw keratocysts, clinical examination and radiographs should nearly always establish the diagnosis of NBCCS. In addition to examination of the child, a medical history and examination of the parents is advised.

Medulloblastoma

Children presenting with medulloblastoma need to be assessed for NBCCS, particularly if they are younger than age three years and/or have desmoplastic histology. In addition to examining the child, a medical history and examination of the parents is advised.

Children with nodular or desmoplastic medulloblastoma also need to be assessed for a germline heterozygous pathogenic variant in *SUFU* [Brugières et al 2012]. Brugières and colleagues found that 3/3 individuals with nodular medulloblastoma and 4/20 individuals with desmoplastic medulloblastoma caused by a germline heterozygous pathogenic variant in *SUFU* had some features of NBCCS. Furthermore, a germline pathogenic variant in *SUFU* is associated with macrocephaly and 1/8 individuals with an *SUFU* heterozygous germline pathogenic variant who had medulloblastoma developed BCCs in the radiation field [Brugières et al 2012].

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with nevoid basal cell carcinoma syndrome (NBCCS), the following evaluations are recommended if they have not already been completed:

- Baseline measurement of head circumference, preferably plotted on a chart that accounts for height. Evidence of rapid increase in centiles should prompt further investigation to exclude hydrocephalus.
- Physical examination for birth defects of clinical significance (e.g., orofacial clefts, polydactyly)
- X-rays to evaluate for rib and vertebral anomalies and falx calcification
- Ophthalmologic evaluation for evidence of strabismus, cataract, orbital cyst, microphthalmia, and pigmentary changes of the retinal epithelium
- Evaluation by a dentist or orthodontist familiar with NBCCS; jaw x-ray (orthopantogram) in individuals age eight years or older to evaluate for jaw keratocysts and other anomalies
- Skin examination by a dermatologist familiar with NBCCS
- Ultrasound examination of the ovaries to evaluate for ovarian fibromas prior to pregnancy
- Echocardiography in the first year of life to evaluate for cardiac fibromas
- Consultation with a clinical geneticist and/or genetic counselor

Because mesenteric and pleural cysts are rare, evaluation is not necessary in the absence of symptoms.

Treatment of Manifestations

Manifestations should be treated by specialists (e.g., oral surgeon, dermatologist, plastic surgeon, pediatrician, clinical geneticist) experienced with the condition.

- Keratocysts usually require surgical excision.
- Early treatment of BCCs is essential to prevent long-term cosmetic problems, particularly on the face. The priorities are to ensure complete eradication of aggressive BCCs, and to preserve normal tissue to prevent disfigurement. Surgical excision is supplemented by a number of other possible treatments including cryotherapy and laser treatment for early lesions and photodynamic therapy. Photodynamic therapy is particularly suitable for thin lesions of <2 mm on ultrasound [Basset-Seguin et al 2014]. Surgical treatment using Mohs' microsurgery [Mohs et al 1980] appears particularly effective.

  Systemic treatment with retinoids (e.g., etretinate) is possible but often not well tolerated.

  Treatment of individuals with severe BCC manifestations and/or advanced lesions with sonic hedgehog inhibitors such as vismodegib is now possible; although side effects are common and quite severe, there is a high resolution of advanced lesions and reduction in new BCCs [Sekulic et al 2012]. Sonic hedgehog inhibitors may be particularly helpful with lesions around the eyes [Ozgur et al 2015]. However, the cost of treatment has meant that the National Institute for Health and Care Excellence (NICE) in the UK has judged the treatment not cost effective.
- Cardiac fibromas may be asymptomatic and can be monitored by a pediatric cardiologist.
- If ovarian fibromas require surgical treatment, preservation of ovarian tissue is recommended, although it involves a risk of recurrence [Seracchioli et al 2001].

Prevention of Primary Manifestations

Affected individuals should avoid UV exposure and cover up exposed skin by wearing long sleeves, high collars, and hats; complete sunblock should be used.

Avoid unnecessary radiation exposure from the environment, investigative radiology, or radiotherapy treatment.

Surveillance

Head circumference should be followed throughout childhood and plotted on appropriate growth charts. Rapid enlargement should prompt evaluation for possible hydrocephalus.

Awareness of the risk of medulloblastoma in the first years of life is important and may justify developmental assessment and physical examination every six months. No evidence for the efficacy of regular neuroimaging exists; frequent computed tomography scans should be avoided because of risks associated with radiation sensitivity. A consensus meeting has suggested annual head MRI scans until age eight years in affected children [Bree et al 2011], but this would require general anesthesia for many children and is probably not now justified in *PTCH1*-related NBCCS with only a 2% risk [Foulkes et al 2017]. However, it may well be justified in infants with *SUFU* pathogenic variants [Smith et al 2014]; this has been supported by a consensus statement recommendation to "consider brain MRI every four months through age three years, then brain MRI every six months until the age five years" [Foulkes et al 2017].

A baseline heart ultrasound examination in infants has been advocated by Foulkes et al [2017].

Ovarian ultrasound in women at age 18 has been advocated by Foulkes et al [2017].

No other tumors occur at a frequency that warrants surveillance above that offered to members of the general population.

Orthopantogram is indicated every 12-18 months in individuals older than age eight years to identify jaw keratocysts [Foulkes et al 2017].

Skin should be examined at least annually; some physicians recommend skin examination by a professional every three to four months.

Agents/Circumstances to Avoid

Use of radiotherapy can lead to the development of thousands of BCCs in the radiation field [Strong 1977, Evans et al 1991a] and therefore should be avoided if there are alternative treatments, especially in childhood. If the treating team believes that no other treatment modality is possible, radiotherapy should be used through as few skin ports as possible.

Diagnostic x-rays should be used sparingly.

Individuals with NBCCS should be advised to avoid direct sun exposure as much as possible. Excessive sun exposure increases the likelihood of developing BCCs.

Evaluation of Relatives at Risk

It is appropriate to evaluate apparently asymptomatic older and younger at-risk relatives (including children) of an affected individual in order to identify as early as possible those who would benefit from surveillance (see Surveillance) for complications of NBCCS (most notably medulloblastoma in children and jaw cysts and BCCs in adults) and avoidance of x-rays and sun exposure (see Agents/Circumstances to Avoid).

Evaluations can include:

- Molecular genetic testing if the pathogenic variant in the family is known;
- Clinical examination and x-rays of the skull for calcification if the pathogenic variant in the family is not known; these may be less likely to clarify the genetic status in a very young child because of the age-related features of NBCCS.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

Since individuals with NBCCS have a large head circumference, a woman who is carrying an affected fetus should be assessed for the need for either early induction of labor or cesarean section delivery due to cephalopelvic disproportion.

Therapies Under Investigation

Photodynamic therapy (with infra-red light) showed early promise and appears safe [Haylett et al 2003]. A recent study showed outcomes in 33 individuals with NBCCS treated with photodynamic therapy (PDT) with a near-60% control rate [Loncaster et al 2009].

Aminolevulinic acid has been investigated [Itkin & Gilchrest 2004, Oseroff et al 2005]. It is usually used in conjunction with PDT [Loncaster et al 2009].

Topical treatment with 5-fluorouracil (Efudex®) or imiquimod (5%) has been investigated [Kagy & Amonette 2000, Marks et al 2001, Stockfleth et al 2002]. A recent review suggested control rates approaching 90% for superficial BCCs and 50% for aggressive or nodular BCCs with imiquimod [Alessi et al 2009].

Topical 5-fluorouracil appears effective for superficial multicentric BCCs without follicular involvement but should not be used for deeply invasive BCCs.

Recently topical use of sonic hedgehog antagonists has entered clinical trials and is showing promise [Saran 2010]. Systemic use of sonic hedgehog antagonists in individuals with NBCCS who have advanced or refractory BCCs has also been effective [Sekulic et al 2012, Tang et al 2012], with a 43% response rate in 63 affected individuals with locally advanced BCCs. Response rates were very high in individuals with NBCCS but 53% discontinued therapy because of adverse side effects [Tang et al 2012]. Sonic hedgehog antagonists may be particularly useful for periocular lesions [Ozgur et al 2015]. A recent report suggests that anti-sonic hedgehog agents may also resolve keratocysts when given for BCC treatment [Goldberg et al 2011].

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

Genetic Counseling

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

Mode of Inheritance

Nevoid basal cell carcinoma syndrome (NBCCS) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Approximately 70%-80% of individuals diagnosed with NBCCS have an affected parent.

- A proband with NBCCS may have the disorder as the result of a *de novo PTCH1* or *SUFU* pathogenic variant. The proportion of individuals with NBCCS with a *de novo* pathogenic variant is approximately 20%-30%.
- If the pathogenic variant found in the proband cannot be detected in leukocyte DNA of either parent, two possible explanations are germline mosaicism in a parent or a *de novo* pathogenic variant in the proband.
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* pathogenic variant include a detailed skin examination, AP and lateral x-rays of the skull, chest x-ray, and spine x-ray. Molecular genetic testing can be used to clarify the genetic status of a parent when a *PTCH1* or *SUFU* pathogenic variant has been identified in the proband or other affected family member.
- The family history of some individuals diagnosed with NBCCS may appear to be negative as a result of failure to recognize the disorder in a family member, early death of the parent before the onset of symptoms, or late onset of the disorder in the affected parent. Therefore, an apparently negative family history cannot be confirmed unless appropriate clinical evaluation and/or molecular genetic testing has been performed on the parents of the proband.
- Note: If the parent is the individual in whom the pathogenic variant first occurred, s/he may have somatic mosaicism for the pathogenic variant, and may be mildly/minimally affected.

Sibs of a proband

- The risk to the sibs of the proband depends on the genetic status of the proband's parents.
- If a parent of the proband is affected, the risk to the sibs is 50%.
- When the parents are clinically unaffected, the risk to the sibs of a proband appears to be low.
- If the *PTCH1* or *SUFU* pathogenic variant cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the possibility of parental germline mosaicism [Rahbari et al 2016]. Although parental germline mosaicism has not been reported in NBCCS, low risks have been confirmed in the analogous situation in individuals with neurofibromatosis type 2 [Evans et al 2007].

Offspring of a proband

- Each child of an individual with NBCCS has a 50% chance of inheriting the *PTCH1* or *SUFU* pathogenic variant.
- The offspring of an individual with mild NBCCS caused by somatic mosaicism may have a less than 50% chance of inheriting the pathogenic variant.

Other family members. The risk to other family members depends on the genetic status of the proband's parents: if a parent is affected, his or her family members may be at risk.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Genetic cancer risk assessment and counseling. For comprehensive descriptions of the medical, psychosocial, and ethical ramifications of identifying at-risk individuals through cancer risk assessment with or without molecular genetic testing, see , see Cancer Genetics Risk Assessment and Counseling – for health professionals (part of PDQ®, National Cancer Institute).

Considerations in families with an apparent *de novo* pathogenic variant. When neither parent of a proband with NBCCS has the pathogenic variant or clinical evidence of the disorder, the *PTCH1* or *SUFU* pathogenic variant is likely *de novo*. However, possible non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) or undisclosed adoption can also be explored.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

Predictive testing of individuals during childhood. Because of the need for surveillance for complications of NBCCS (most notably medulloblastoma) during childhood, clarification of the genetic status of at-risk individuals during childhood is appropriate. Clinical examination and x-rays of the skull for calcification may be less likely to clarify the genetic status in a very young child because of the age-related nature of features in NBCCS. Molecular genetic testing may be considered if a *PTCH1* or *SUFU* pathogenic variant has been identified in an affected family member.

Predictive testing of adults. Clinical examination and x-rays frequently act as a "genetic test" in an apparently unaffected individual. Individuals need to be aware of the predictive implications of these examinations as well as those of molecular genetic testing of *PTCH1* or *SUFU*.

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

Prenatal Testing and Preimplantation Genetic Testing

Once the *PTCH1* or *SUFU* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for nevoid basal cell carcinoma syndrome are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

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

- **BCCNS Life Support Network**
  14525 North Cheshire Street
  PO Box 321
  Burton OH 44021
  Phone: 866-834-1895 (toll-free); 440-834-0011
  Fax: 440-834-0132
  Email: info@bccns.org
  www.gorlinsyndrome.org
- **Gorlin Syndrome Group**
  www.gorlingroup.org
- **My46 Trait Profile**
  Nevoid basal cell carcinoma syndrome

Molecular Genetics

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

Table A. Nevoid Basal Cell Carcinoma Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
PTCH1	9q22.32	Protein patched homolog 1	PTCH1 database	PTCH1	PTCH1
SUFU	10q24.32	Suppressor of fused homolog	SUFU database	SUFU	SUFU

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

Table B. OMIM Entries for Nevoid Basal Cell Carcinoma Syndrome (View All in OMIM)

109400	BASAL CELL NEVUS SYNDROME; BCNS
601309	PATCHED 1; PTCH1
607035	SUFU NEGATIVE REGULATOR OF HEDGEHOG SIGNALING; SUFU

Molecular Pathogenesis

The comparatively young mean age at onset of medulloblastoma in individuals with nevoid basal cell carcinoma syndrome (NBCCS) (age 2 years vs 7 years in the general population) and the loss of the normal *PTCH1* allele in tumors [Cowan et al 1997] confirm *PTCH1* as a tumor suppressor in medulloblastoma as well as in basal cell carcinoma (BCC). Inactivation of the normal allele also appears to be the mechanism responsible for jaw cysts, whereas the congenital malformations are likely to result from alterations in the concentration of the protein patched homolog 1 in the extremely dosage-sensitive hedgehog signaling pathway [Villavicencio et al 2000].

Note: *PTCH2*, highly homologous to *PTCH1*, was mapped to chromosome 1p32.1-p32.3 [Smyth et al 1999]. No *PTCH2* pathogenic variants were found in 11 simplex cases of NBCCS or in 11 individuals with familial cases of NBCCS who did not have identifiable *PTCH1* pathogenic variants. Nonetheless occasional case reports of *PTCH2* variants in NBCCS have been recorded [Fujii et al 2013].

PTCH1

Gene structure. The *PTCH1* transcript variant NM_000264.4 has 24 exons and encodes the longest protein isoform NP_000255.2. Alternative splicing results in multiple transcript variants that encode different protein isoforms. For a detailed summary of gene, transcript and protein information, see Table A, **Gene**.

Pathogenic variants. See Table 2.

Table 2. Frequency of Types of Pathogenic Variants of *PTCH1*

% of Individuals with NBCCS and Pathogenic *PTCH1* Variants		Type of Pathogenic Variant
See footnote 1	Evans et al [2017] [2]	
65%	40%	Premature termination codon (predicting a protein truncation)
16%	27%	Missense
13%	20%	Splice site

Table 2. continued from previous page.

% of Individuals with NBCCS and Pathogenic *PTCH1* Variants		Type of Pathogenic Variant
See footnote 1	Evans et al [2017] [2]	
6%	13%	(Multi)exon or large-scale deletions or rearrangements
Rare [3]	1%	Deep intronic variants that alter splicing

1. Source: literature and 395 samples from diagnostic laboratory, Birmingham Women's Hospital, UK, August 2007 (Proportions of types of pathogenic variant have remained the same over several years.)
2. n=126
3. Bholah et al [2014]

Normal gene product. The protein isoform NP_000255.2 has 1447 amino acids. Protein patched homolog 1 is an integral membrane protein with 12 transmembrane regions, two extracellular loops, and a putative sterol-sensing domain. Protein patched homolog 1 binds the secreted factor sonic hedgehog (SHH) and functions as the SHH receptor. The protein represses the signaling activity of the co-receptor smoothened (SMO). When in complex with SHH, protein patched homolog 1 is not a repressor, and signaling ensues. At least three forms of the protein patched homolog 1 are present in human cells [Hahn et al 1996]. The suppression of SHH signaling pathway through SMO has been the target of inhibitor drug therapies that partly mimic the loss of PTCH1 function [Skoda et al 2018].

Abnormal gene product. Pathogenic variants found in individuals with NBCCS and nonfamilial BCC include those predicted to result in a truncated protein and missense variants. Rare deep intronic variants that alter splicing are predicted to cause loss of function of protein patched homolog 1 [Bholah et al 2014].

SUFU

Gene structure. Alternative splicing results in multiple transcript variants. The longest, comprising 12 exons, is NM_016169.3. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. Missense and nonsense variants, splice consensus sites, and multiexon deletions have been reported [Kijima et al 2012, Smith et al 2014].

Normal gene product. *SUFU* encodes the suppressor of fused homolog protein, which is a negative regulator in the hedgehog signaling pathway. The NM_016169.3 transcript variant encodes the longer isoform NP_057253.2 with 484 amino acid residues.

Abnormal gene product. Heterozygous loss-of-function variants in *SUFU* cause NBCCS.

Cancer and Benign Tumors

Somatic variants in *PTCH1* are involved in a range of sporadically occurring tumors including those observed in NBCCS: keratocysts, BCC, skin trichoepithelioma, medulloblastoma, and ovarian fibroma.

SUFU pathogenic variants are usually germline in individuals with medulloblastoma but can occur somatically (far less so than *PTCH1*) and when present confer resistance to SMO inhibition [Kool et al 2014].

Somatic *PTCH2* pathogenic variants were found in one simplex case (i.e., a single occurrence of the disease in a family) of medulloblastoma and one of BCC with the latter not present in the germline [Smyth et al 1999].

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Chapter Notes

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