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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. Many 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 90% of affected individuals by age 30 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 proposed diagnostic clinical criteria. Identification of a heterozygous germline pathogenic variant in *PTCH1* or *SUFU* by molecular genetic testing establishes the diagnosis if clinical features are inconclusive.

Management

Treatment of manifestations: Best provided by specialists experienced with the condition; avoidance of direct sun exposure through the use of complete sunblock and covering of exposed skin with long sleeves, high collars, and hats; 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; jaw keratocysts usually require surgical excision; treatment of medulloblastoma per neurosurgeon/oncologist.

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Surveillance: Monitor head circumference throughout childhood; ophthalmology evaluations per ophthalmologist; feeding, hearing, and speech evaluation as needed in those with a history of cleft lip/palate; clinical exam for scoliosis as needed; skin examination at least annually; orthopantogram every 12-18 months beginning at age eight years to identify jaw keratocysts; developmental assessment and physical examination every six months until age five years due to increased risk for medulloblastoma; brain MRI in those with *SUFU*-related NBCCS every three to four months until age three years, every six months until age five years, annually until age eight years for medulloblastoma, and then every three to five years beginning at age 30 years for meningioma; ovarian ultrasound in women at age 18 years.

Agents/circumstances to avoid: Radiotherapy if there are alternative treatments, especially in childhood; diagnostic radiographs should be used sparingly; direct sun exposure should be limited, as 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 keratocysts and BCCs in adults) and the need to avoid radiographs and 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. Each child of an individual with NBCCS has a 50% chance of inheriting the disorder. If the NBCCS-related pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing for NBCCS are possible.

Diagnosis

No consensus clinical diagnostic criteria for nevoid basal cell carcinoma syndrome (NBCCS) have been published. Diagnostic criteria for NBCCS have been proposed [Evans et al 1993, Kimonis et al 1997].

Suggestive Findings

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. Note: Falx calcification is nearly always present on AP skull radiographs after age 20 years in those with NBCCS.
- **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 skin (that burns easily and does not tan) 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 diagnosis of 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 [2011] criteria [Foulkes et al 2017].

- Lymphomesenteric or pleural cysts
- Macrocephaly (OFC >97th centile)
- Cleft lip/palate
- Rib/vertebral anomalies observed on chest and/or spine radiograph: bifid/splayed/extra ribs, bifid vertebrae

  Note: (1) To verify a clinical diagnosis of NBCCS, AP and lateral radiographs of the skull, an orthopantogram, chest radiograph, and spine radiograph are usually necessary. (2) Radiographs should be avoided in children if they are not needed to confirm the diagnosis of NBCCS. (3) If radiographs have been taken previously (i.e., before the diagnosis of NBCCS is being considered), providers should obtain and review the original radiographs rather than repeat them because individuals with NBCCS are susceptible to x-irradiation. (4) 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. (5) Radiographic findings may be helpful in suggesting or confirming the diagnosis in young children with cardiac fibromas, cleft lip/palate, polydactyly, or macrocephaly.

- Preaxial or postaxial polydactyly
- Ovarian/cardiac fibromas
- Ocular anomalies (e.g., cataract, developmental defects, and pigmentary changes of the retinal epithelium)

Establishing the Diagnosis

The clinical diagnosis of NBCCS can be **established** in a proband based on proposed clinical diagnostic criteria [Evans et al 1993, Kimonis et al 1997], or the molecular diagnosis can be **established** in a proband with suggestive findings and a heterozygous pathogenic (or likely pathogenic) variant in *PTCH1* or *SUFU* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (2) Identification of a heterozygous *PTCH1* or *SUFU* variant of uncertain significance does not establish or rule out the diagnosis.

Clinical Diagnosis

A clinical diagnosis of NBCCS **can be established** in a proband with two major diagnostic criteria and one minor diagnostic criterion or one major and three minor diagnostic criteria [Evans et al 1993] (see Suggestive

Findings). 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.

Note: Some clinical features of NBCCS only become apparent with increasing age (e.g., BCCs, jaw keratocysts, ectopic calcifications, meningioma, and gonadal tumors). Clinical diagnostic criteria may be more informative in adults with NBCCS [Guerrini-Rousseau et al 2018].

Molecular Diagnosis

The molecular diagnosis of NBCCS **is established** in a proband with suggestive findings and 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: Identification of an identical *PTCH1* pathogenic variant in two or more separate tumors but not present in lymphocyte DNA (or present at a variant allele fraction of <50%) confirms mosaicism for *PTCH1*-related NBCCS [Evans et al 2007].

Molecular testing approaches can include a combination of **gene-targeted testing** (concurrent gene testing, serial single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing). Gene-targeted testing requires that the clinician determine which gene(s) are likely involved (see Option 1), whereas comprehensive genomic testing does not (see Option 2).

Option 1

Concurrent gene testing. In those with suspected NBCCS, sequence analysis of *PTCH1* and *SUFU* can be performed first to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If no variant is detected by the sequencing method used, the next step is to perform *PTCH1* and *SUFU* deletion/duplication analysis to detect exon and whole-gene deletions or duplications.

Serial single-gene testing. Sequence analysis and gene-targeted deletion/duplication analysis of *PTCH1* can be considered first in individuals with a personal or family history of jaw keratocysts. *SUFU* molecular testing should be considered first in individuals 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 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 most likely to identify the genetic cause of condition 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.

Option 2

When the diagnosis of NBCCS has not been considered because an individual has atypical phenotypic features, **comprehensive genomic testing** does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

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]	Proportion of NBCCS Attributed to Pathogenic Variants in Gene	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method	
		Sequence analysis [3]	Gene-targeted deletion/ duplication analysis [4]
PTCH1	67%-79%	50%-85% [5, 6]	6%-21% [6]
SUFU	~6%	5% [6]	~1% [6]
Unknown	15%-27% [7, 8]	NA	

NA = not applicable; NBCCS = nevoid basal cell carcinoma syndrome
1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications. Exome and genome sequencing may be able to detect deletions/duplications using breakpoint detection or read depth; however, sensitivity can be lower than gene-targeted deletion/duplication analysis.
5. PTCH1 deep intronic pathogenic variants that alter splicing have been identified; sequence analysis that detects these deep intronic variants should be considered [Bholah et al 2014].
6. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
7. PTCH2 pathogenic variants have been reported in individuals with NBCCS [Fujii et al 2013]. This finding has not been confirmed on subsequent studies [Smith & Evans 2022].
8. Heterozygous germline pathogenic variants in *GPR161* and *ELP1* have been reported in individuals with pediatric medulloblastoma. One individual with a *GPR161* pathogenic variant had minimal features of NBCCS [Begemann et al 2020] (see Differential Diagnosis). An additional 27 individuals with a clinical diagnosis of NBCCS (and no *PTCH1* or *SUFU* pathogenic variant identified) were not found to have a pathogenic variant in either *GPR161* or *ELP1* [Smith et al 2023].

Clinical Characteristics

Clinical Description

Nevoid basal cell carcinoma syndrome (NBCCS) is characterized by macrocephaly, characteristic facial features, congenital rib/vertebral anomalies, ectopic calcification of the falx, basal cell carcinoma, and an increased risk of medulloblastoma and other tumors. To date, more than 500 individuals have been identified with *PTCH1*-related NBCCS and 176 individuals have been identified with *SUFU*-related NBCCS [Pál et al 2023, Lee et al 2024]. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. Nevoid Basal Cell Carcinoma Syndrome: Frequency of Select Features

Feature		% of Persons w/Feature		Comment
		PTCH1-related NBCCS	*SUFU*-related NBCCS	
Craniofacial features	Macrocephaly	>90%	>60%	Typically >97th centile by age 10-18 mos
	Characteristic facial features	~60%	Less frequent than in *PTCH1*-related NBCCS	Frontal bossing, hypertelorism, coarse facial features, & facial milia
	Eye findings	>60%	Unknown	Strabismus, cataract, nystagmus, coloboma
	Cleft lip/palate	5%	NR	
Skeletal features	Congenital rib/vertebral anomalies	60%	Less frequent than in *PTCH1*-related NBCCS	Bifid ribs, wedge-shaped vertebrae, polydactyly
	Ectopic calcification	90% by age 30 yrs	Likely similar to *PTCH1*-related NBCCS	Typically of the falx
	Polydactyly	1%	Unknown	
Tumors	Basal cell carcinoma	90%	<90%	Typical onset is late teens or early adulthood; onset can be in childhood
	Jaw keratocysts	~90%	NR	
	Medulloblastoma	<2%	Up to 20%-33%	
	Meningioma	<2%	11%	
	Cardiac fibroma	2%	NR	
	Ameloblastoma	Rare	NR	Tumor developing from jaw keratocyst

Based on Evans et al [2017]
NBCCS = nevoid basal cell carcinoma syndrome; NR = to date, this feature has not been reported in this group

Craniofacial Features

Macrocephaly. The first feature likely to be observed is macrocephaly. A large proportion of babies with NBCCS require delivery by cesarean section because of large head size; most infants have head circumference >97th centile at birth. 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.

Facies. Approximately 60% of individuals with a *PTCH1* pathogenic variant have a recognizable appearance. Frontal bossing, hypertelorism, and coarse facial features develop after puberty, and facial milia are present post infancy. Facial features are likely more subtle in individuals with *SUFU*-related NBCCS.

Eye findings include strabismus (63%), congenital cataract (18%), nystagmus (9%), and colobomas (9%). Orbital cyst, microphthalmia, and pigmentary changes of the retinal epithelium are less common eye findings [Black et al 2003, Ragge et al 2005, Moramarco et al 2019].

Cleft lip/palate is reported in 5% of individuals but is not reported thus far in individuals with *SUFU*-related NBCCS.

Skeletal Features

Congenital rib/vertebral anomalies are present at birth but are not clinically apparent 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 90% of individuals by age 30 years. Sella calcification, when present, is visible on lateral radiographs of the skull.

Polydactyly (typically postaxial) can occur in individuals with NBCCS [Acharya et al 2013].

Tumors

Basal cell carcinomas (BCCs). Brownish/pink/orange basal cell nevi may occur in early childhood; basal cell nevi may be numerous and may be quiescent without evidence of aggressive behavior. BCCs can occur in early childhood, but in general do not present until the late teens or early adulthood. The histologic appearance is that of a typical BCC, which can be the first identified feature of NBCCS in simplex cases (i.e., affected individuals with no known family history of NBCCS), especially in children. BCCs may grow from existing basal cell nevi or may appear from blemish-free skin. BCCs may also crust, bleed, and ulcerate, or may present as a localized infection.

BCCs 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) and individuals with excessive ultraviolet light exposure seem especially prone to developing large numbers of BCCs. Some affected individuals appear to be particularly radiosensitive, with new BCCs appearing in the field of radiation following radiotherapy.

Jaw keratocysts (keratocystic odontogenic tumors). 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 keratocysts rarely occur after age 30 years.

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

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

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

SUFU-related NBCCS is associated with a high risk for medulloblastoma of up to 33% (3/9) and a high meningioma risk post radiation [Smith et al 2014]. The risk for medulloblastoma in *PTCH1*-related NBCCS is less than 2% [Smith et al 2014].

Cardiac tumors. Cardiac fibromas occur in approximately 2% of individuals with NBCCS [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.

Gonadal tumors. Ovarian fibromas occur in approximately 20% of females with NBCCS [Evans et al 1993, Gorlin 2004]. They 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. Gonadal teratoma and testicular fibrosarcoma have also been reported in individuals with *SUFU*-related NBCCS [Guerrini-Rousseau et al 2022].

Meningioma. Meningiomas occur in around 2% of individuals with *PTCH1*-related NBCCS and 11%-30% of individuals with *SUFU*-related NBCCS [Evans et al 2017, Lee et al 2024].

Other tumors. The risk of other malignant tumors is not clearly increased, although lymphoma has been reported [Pereira et al 2011]. Rhabdomyoma of the tongue has also been reported in a fetus with NBCCS [Watson et al 2004].

Other Reported Features

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.

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.

Mesenteric and pleural cysts are rarely reported and do not often result in clinical manifestations [Evans et al 2017].

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, 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 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 keratocysts (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 individuals with *PTCH1*-related NBCCS was less 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 following radiation treatment.

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 fewer BCCs and no jaw keratocysts reported [Evans et al 2017].

Individuals with a heterozygous germline *SUFU* pathogenic variant have been reported with meningioma or meningioblastoma and minimal or no additional features of NBCCS. Additional cancers reported in individuals with a *SUFU* heterozygous germline pathogenic variant have included early-onset breast cancer and leiomyosarcoma [Taylor et al 2002, Brugières et al 2010]. Because several clinical features of NBCCS are age

dependent, it is not clear if these individuals will develop additional features of NBCCS with time. Affected individuals from one family described with *SUFU*-related meningioma also developed an ovarian tumor and a basal cell tumor [Aavikko et al 2012].

Genotype-Phenotype Correlations

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

Penetrance

Although NBCCS shows intra- and interfamilial variation in expression, experience clinically and from molecular testing is compatible with complete penetrance for *PTCH1*-related NBCCS, although with more subtle features in those with missense pathogenic variants [Author, personal observation]. The penetrance of *SUFU* pathogenic variants appears to be reduced.

Prevalence

The prevalence of NBCCS is reported to be between 1:18,976 and 1:30,827 [Evans et al 2010]. The true prevalence may be higher, as individuals with milder features may not be recognized.

Genetically Related (Allelic) Disorders

PTCH1

- A non-recurrent contiguous gene deletion at chromosome 9q22.3 encompassing a 352-kb critical region including *PTCH1*, *FANCC*, and adjacent genes 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, seizures, and in 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 deletion [Beltrami et al 2020].
- **Sporadic tumors.** Somatic variants in *PTCH1* are involved in a range of sporadically occurring tumors including those observed in NBCCS: keratocysts, basal cell carcinoma (BCC), skin trichoepithelioma, medulloblastoma, and ovarian fibroma. In these circumstances predisposition to these tumors is not heritable.

SUFU

- ***SUFU*-related neurodevelopmental disorder.** Heterozygous germline *SUFU* pathogenic variants have been reported in individuals with Joubert syndrome and congenital ocular motor apraxia [Serpieri et al 2022]. To date, features reported in *SUFU*-related NBCCS have not been reported in individuals with *SUFU*-related neurodevelopmental disorder.
- **Sporadic tumors** (including medulloblastoma and BCC) occurring as single tumors in the absence of any other findings of NBCCS may contain a somatic pathogenic variant in *SUFU* that is **not** present in the germline [Kool et al 2014]. In these circumstances predisposition to these tumors is not heritable.

Note: Pathogenic variants in *PTCH1* and *SUFU* have been reported in individuals with nonsyndromic holoprosencephaly (HPE). However, because investigations of several large HPE cohorts have failed to reproduce these findings, more data may be needed to confirm the possible role of these genes in HPE pathogenesis. (See Holoprosencephaly Overview.)

Differential Diagnosis

Table 3. Genes of Interest in the Differential Diagnosis of Nevoid Basal Cell Carcinoma Syndrome

Gene / Genetic Mechanism	Disorder	MOI	Features of Disorder	
			Overlapping w/NBCCS	Distinguishing from NBCCS
CYLD	Brooke-Spiegler syndrome	AD	• Milia • BCC	• Trichoepitheliomas & cylindromas • Absence of macrocephaly & other congenital & skeletal features of NBCCS
ELP1	*ELP1*-related pediatric medulloblastoma [1]	AD	Medulloblastoma	Absence of macrocephaly & other congenital & skeletal features of NBCCS
GPR161	*GPR161*-related pediatric medulloblastoma [1, 2]	AD	• Multiple BCCs • Medulloblastoma • Meningioma • Frontal bossing	• Multinodular thyroid goiter • GI polyposis • GI adenoma
NSD1	Sotos syndrome	AD	• Macrocephaly • DD	• Broad & prominent forehead, dolichocephaly, sparse frontotemporal hair, downslanting palpebral fissures, long & narrow face • Mild-to-severe ID • Risk of other types of tumors not reported in NBCCS
PTEN	*PTEN* hamartoma tumor syndrome	AD	Macrocephaly	• Skin features such as trichilemmoma • Lhermitte-Duclos disease
Xq26 duplication	Bazex-Dupre-Christol syndrome (OMIM 301845)	XL	Multiple BCCs	• Follicular atrophoderma on the dorsum of hands & feet, ↓ sweating, & hypotrichosis • Pitting on backs of hands is reminiscent of orange peel & quite unlike palmar & plantar pits of NBCCS. • Absence of macrocephaly & other congenital & skeletal features of NBCCS

AD = autosomal dominant; BCC = basal cell carcinoma; DD = developmental delay; GI = gastrointestinal; ID = intellectual disability; MOI = mode of inheritance; NBCCS = nevoid basal cell carcinoma syndrome; XL = X-linked

1. Although increased risk of medulloblastoma is reported in individuals with a germline pathogenic variant in *ELP1* or *GPR161*, the overall risks are below 1% [Smith et al 2023].

2. One individual with a *GPR161* pathogenic variant had minimal features of NBCCS; several additional individuals were only reported to have childhood-onset medulloblastoma [Begemann et al 2020].

Rombo syndrome, a dominantly inherited condition similar to Bazex-Dupre-Christol syndrome, has been reported in a single family (OMIM 180730). Skin findings are vermiculate atrophoderma, milia, hypotrichosis, trichoepitheliomas, basal cell carcinomas (BCCs), and peripheral vasodilation with cyanosis. The skin is normal until later childhood; BCCs develop in adulthood. Sweating is normal.

Acquired causes of multiple BCCs include arsenic exposure.

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 evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Nevoid Basal Cell Carcinoma Syndrome: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Macrocephaly	Baseline head circumference, preferably plotted on a chart that accounts for height	Evidence of rapid increase in centiles should prompt further investigation to exclude hydrocephalus.
Eye manifestations	Ophthalmologic eval for evidence of strabismus, cataract, orbital cyst, microphthalmia, & pigmentary changes of retinal epithelium	
Congenital anomalies (orofacial clefts, rib/vertebral anomalies, polydactyly)	Physical exam for birth defects of clinical significance (e.g., orofacial clefts, spine abnormalities, polydactyly)	
BCCs	Skin exam by dermatologist familiar w/NBCCS	
Jaw keratocysts	• Eval by dentist or orthodontist familiar w/ NBCCS • Jaw radiograph (orthopantogram)	In persons age ≥8 years to evaluate for jaw keratocysts & other anomalies
Medulloblastoma	Brain MRI w/contrast	
Cardiac tumors	Echocardiography to evaluate for cardiac fibromas	In 1st yr of life [1]
Ovarian fibromas	Ultrasound exam of ovaries to evaluate for ovarian fibromas	In women at age 18 yrs [1]
Genetic counseling	By genetics professionals [2]	To inform affected persons & their families re nature, MOI, & implications of NBCCS to facilitate medical & personal decision making

BCC = basal cell carcinoma; MOI = mode of inheritance; NBCCS = nevoid basal cell carcinoma syndrome
1. Foulkes et al [2017]
2. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Manifestations should be treated by specialists (e.g., ophthalmologist, orthopedist, dermatologist, plastic surgeon, oral surgeon, neurosurgeon, oncologist, gynecologist) experienced with the condition (see Table 5).

Table 5. Nevoid Basal Cell Carcinoma Syndrome: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Macrocephaly	Rarely, treatment for hydrocephalus is indicated.	
Eye manifestations	Treatment per ophthalmologist	
Orofacial clefts	Treatment per craniofacial specialists	
Skeletal anomalies: rib/vertebral anomalies, polydactyly	Treatment per orthopedist as needed	
BCCs	Education re prevention of BCCs:	

Table 5. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
	• Avoid direct sun exposure. • Cover up exposed skin by wearing long sleeves, high collars, & hats. • Complete sunblock should be used.	
	Treatment options incl surgical excision, cryotherapy, laser treatment for early lesions, photodynamic therapy, & sonic hedgehog inhibitors (e.g., vismodegib). [1] • Surgical treatment using Mohs microsurgery [2] appears particularly effective. • Photodynamic therapy is particularly suitable for thin lesions of <2 mm on ultrasound. [3] • Treatment of severe &/or advanced BCCs w/sonic hedgehog inhibitors (e.g., vismodegib) is particularly helpful w/lesions around the eyes, [4] although side effects are common & quite severe. Due to high cost of treatment, NICE in the UK has judged the treatment not cost effective.	Early treatment is essential to prevent long-term cosmetic problems, particularly on the face. The priorities are to ensure complete eradication of aggressive BCCs, & to preserve normal tissue to prevent disfigurement.
Jaw keratocysts	Keratocysts usually require surgical excision.	
Medulloblastoma	Treatment per neurosurgeon/oncologist	
Cardiac tumors	Cardiac fibromas may be asymptomatic & can be monitored by a pediatric cardiologist.	
Ovarian fibromas	If ovarian fibromas require surgical treatment, preservation of ovarian tissue is recommended, although it involves a risk of recurrence. [5]	

BCC = basal cell carcinoma; NICE = National Institute for Health and Care Excellence; UK = United Kingdom
1. Systemic treatment of BCCs with retinoids (e.g., etretinate) is possible but often not well tolerated.
2. Mohs et al [1980]
3. Basset-Seguin et al [2014]
4. Ozgur et al [2015]
5. Seracchioli et al [2001]

Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations summarized in Table 6 are recommended.

Table 6. Nevoid Basal Cell Carcinoma Syndrome: Recommended Surveillance

System/Concern	Evaluation	Frequency
Macrocephaly	• Assess head circumference using gender- & ethnicity-specific growth charts. • Rapid enlargement of head circumference should prompt eval for possible hydrocephalus.	At each visit throughout childhood
Eye manifestations	Ophthalmology eval	Frequency per ophthalmologist
Orofacial clefts	Feeding, hearing, & speech evals in those w/ history of clefts	Frequency per ENT or craniofacial specialist

Table 6. continued from previous page.

System/Concern	Evaluation	Frequency
Scoliosis	Clinical exam for scoliosis in those w/vertebral anomalies	As needed
BCCs	Skin exam by dermatologist for BCCs	At least annually; consider every 3-4 mos
Jaw keratocysts	Orthopantogram to identify new jaw keratocysts	Every 12-18 mos in persons age ≥8 yrs [1]
Medulloblastoma	Consider developmental assessment & physical exam	Every 6 mos until age 5 yrs
	Brain MRI w/o contrast	• In those w/***PTCH1*-related NBCCS:** risk does not warrant screening. • In those w/***SUFU*- related NBCCS:** every 3-4 mos until age 3 yrs, every 6 mos until age 5 yrs, then annually until age 8 yrs [1] • In those w/clinical diagnosis of NBCCS & **no identified pathogenic variant**: risk does not warrant screening.
Meningioma	Brain MRI	In those w/***SUFU*-related NBCCS &:** • **No history of medulloblastoma:** every 3-5 yrs beginning at age 30 yrs • **History of medulloblastoma:** frequency per neurosurgeon/oncologist
Cardiac tumors	Follow-up imaging only if recommended by cardiologist	
Ovarian fibromas	Ovarian ultrasound	In women at age 18 yrs [1]
Other tumors	No other tumors occur at a frequency that warrants surveillance above that offered to members of the general population.	

BCC = basal cell carcinoma; ENT = ears, nose, and throat specialist; NBCCS = nevoid basal cell carcinoma syndrome
1. Foulkes et al [2017]

Agents/Circumstances to Avoid

Avoid unnecessary radiation exposure from the environment, investigative radiology, or radiotherapy treatment. Use of radiotherapy can lead to the development of thousands of basal cell carcinomas (BCCs) in the radiation field [Strong 1977, Evans et al 1991] 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 radiographs should be used sparingly.

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 for complications of NBCCS (most notably medulloblastoma in children and jaw cysts and BCCs in adults), early treatment, and avoidance of radiographs and sun exposure (see Agents/Circumstances to Avoid). Evaluations can include:

- Molecular genetic testing if the *PTCH1* or *SUFU* pathogenic variant in the family is known;
- Clinical examination and radiographs 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

Aminolevulinic acid has been investigated for treatment of BCCs [Itkin & Gilchrest 2004, Oseroff et al 2005]. It is usually used in conjunction with photodynamic therapy [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]. Topical 5-fluorouracil appears effective for superficial multicentric BCCs without follicular involvement but should not be used for deeply invasive BCCs. A review suggested control rates approaching 90% for superficial BCCs and 50% for aggressive or nodular BCCs with imiquimod [Alessi et al 2009].

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, mode(s) of 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; it is not meant to address all personal, cultural, or ethical issues that may arise 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%.
- Recommendations for the evaluation of parents of a proband who appears to be the only affected family member (i.e., a simplex case) include a detailed skin examination, anterior to posterior (AP) and lateral radiographs of the skull, chest radiograph, and spine radiograph. Molecular genetic testing can be used to clarify the genetic status of a parent if a *PTCH1* or *SUFU* pathogenic variant has been identified in the proband or other affected family member.

- If the pathogenic variant identified in the proband is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant.
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism.* Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ (gonadal) cells only.

    * A parent with somatic and germline mosaicism for *PTCH1* or *SUFU* pathogenic variant may be mildly/minimally affected.
- 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, late onset of the disorder in the affected parent, or reduced penetrance in a parent heterozygous for a *SUFU* pathogenic variant. Therefore, an apparently negative family history cannot be confirmed without appropriate clinical evaluation of the parents and/or molecular genetic testing (to establish that neither parent is heterozygous for the pathogenic variant identified in the proband).

Sibs of a proband. The risk to the sibs of the proband depends on the clinical/genetic status of the proband's parents:

- If a parent of the proband is affected and/or is known to have the pathogenic variant identified in the proband, the risk to the sibs is 50%.
- If a molecular diagnosis has been established in the proband and the *PTCH1* or *SUFU* pathogenic variant identified in the proband 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].
- If the parents are clinically unaffected but their genetic status is unknown, the risk to the sibs of a proband appears to be low. However, sibs of a proband with clinically unaffected parents are still presumed to be at increased risk for NBCCS because of the possibility of reduced penetrance in a heterozygous parent or parental germline mosaicism.

Offspring of a proband

- Each child of an individual with NBCCS has a 50% chance of inheriting the disorder.
- The offspring of an individual with mild NBCCS caused by somatic mosaicism may have a less than 50% chance of inheriting the pathogenic variant [Reinders et al 2017].

Other family members. The risk to other family members depends on the genetic status of the proband's parents: if a parent is affected and/or known to have a *PTCH1* or *SUFU* pathogenic variant, the parent's 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.

Predictive testing (i.e., testing of asymptomatic at-risk individuals)

- Predictive genetic testing for at-risk asymptomatic family members requires prior identification of the *PTCH1* or *SUFU* pathogenic variant in the family.

- Clinical examination and radiographs frequently act as a "genetic test" in an apparently unaffected individual. (Clinical examination and radiographs 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.) Individuals need to be aware of the predictive implications of these examinations as well as those of molecular genetic testing of *PTCH1* or *SUFU.*
- 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. Parents often want to know the genetic status of their children prior to initiating screening to avoid unnecessary procedures for a child who has not inherited the pathogenic variant. Special consideration should be given to education of the children and their parents prior to genetic testing. A plan should be established for the manner in which results are to be given to the parents and children.

  Potential consequences of such testing (including, but not limited to, socioeconomic changes and the need for long-term follow up and evaluation arrangements for individuals with a positive test result) as well as the capabilities and limitations of predictive testing should be discussed in the context of formal genetic counseling prior to testing.

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 Cancer Genetics Risk Assessment and Counseling – for health professionals (part of PDQ®, National Cancer Institute).

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic 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.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

If the NBCCS-related pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing for NBCCS 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.

- **Gorlin Syndrome Alliance**
  Phone: 267-689-6443

Email: info@gorlinsyndrome.org
www.gorlinsyndrome.org

- **Gorlin Syndrome Group**
  www.gorlingroup.org

Molecular Genetics

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

Table A. 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 1; BCNS1
601309	PATCHED 1; PTCH1
607035	SUFU NEGATIVE REGULATOR OF HEDGEHOG SIGNALING; SUFU

Molecular Pathogenesis

PTCH1 encodes protein patched homolog 1 (PTC1), an integral membrane protein with 12 transmembrane regions, two extracellular loops, and a putative sterol-sensing domain. PTC1 binds the secreted factor sonic hedgehog (SHH) and functions as the SHH receptor. PTC1 represses the signaling activity of the coreceptor smoothened (SMO). When in complex with SHH, PTC1 is not a repressor, and signaling ensues. At least three forms of the PTC1 are present in human cells [Hahn et al 1996]. The suppression of the SHH signaling pathway through SMO has been the target of inhibitor drug therapies that partly mimic the loss of PTC1 function [Skoda et al 2018].

PTCH1 functions as a tumor suppressor in medulloblastoma as well as in basal cell carcinoma. Inactivation of the normal allele also appears to be the mechanism responsible for jaw keratocysts, whereas the congenital malformations are likely to result from alterations in the concentration of PTC1 in the extremely dosage-sensitive hedgehog signaling pathway [Villavicencio et al 2000].

SUFU encodes suppressor of fused homolog (SUFUH), which is a negative regulator in the hedgehog signaling pathway. Similarly to PTC1, loss of SUFUH function leads to upregulation of the pathway and increased risk of medulloblastoma and basal cell carcinoma.

Mechanism of disease causation. Loss of function

Chapter Notes

Author Notes

Dr Miriam Smith (miriam.smith@manchester.ac.uk) is actively involved in clinical research regarding individuals with nevoid basal cell carcinoma syndrome (NBCCS). Dr Smith would be happy to communicate with persons who have any questions regarding diagnosis of NBCCS or other considerations.

Dr Smith is also interested in hearing from clinicians treating families affected by NBCCS in whom no causative variant has been identified through molecular genetic testing of the genes known to be involved in this group of disorders.

Contact Dr Miriam Smith to inquire about review of *PTCH1* or *SUFU* variants of uncertain significance.

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