GENEReviews

Funded by the NIH · Developed at GeneTests (www.genetests.org), University of Washington, Seattle

Nevoid Basal Cell Carcinoma Syndrome

[*Gorlin Syndrome, Basal Cell Nevus Syndrome (BCNS), NBCCS*]

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Initial Posting: June 20, 2002.
Last Update: January 25, 2008.

Summary

Disease 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, bossing of the forehead, 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 children with NBCCS develop medulloblastoma (primitive neuroectodermal tumor [PNET]), generally the desmoplastic subtype. Peak incidence is at age two years. Life expectancy in NBCCS is not significantly different from average.

Diagnosis/testing. In most individuals, the diagnosis of NBCCS is established using clinical diagnostic criteria. *PTCH* is the only gene known to be associated with NBCCS. Molecular genetic testin, available on a clinical basis, detects mutations in the majority of affected individuals.

Management. *Treatment of manifestations:* best provided by specialists experienced with the condition; surgical excision for keratocysts identified early in life; early treatment of BCCs to ensure their complete eradication and to preserve normal tissue to prevent disfigurement; preservation of ovarian tissue whenever ovarian fibromas require surgical treatment. *Prevention of primary manifestations:* avoidance of sun exposure and of x-irradiation. *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 of medulloblastoma; in those over age eight years, orthopantogram every 12-18 months to identify jaw keratocysts; skin examination at least annually. *Agents/circumstances to avoid:* excessive sun exposure; use of radiotherapy because of risk of developing multiple BCCs in the treated area. *Testing 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 probands have inherited the condition from a parent and approximately 20%-30% of probands have a *de novo* mutation. Offspring of an affected individual have a 50% risk of inheriting NBCCS. Prenatal testing for pregnancies at increased risk is possible if the disease-causing mutation has been identified in an affected family member.

Diagnosis

Clinical Diagnosis

Nevoid basal cell carcinoma syndrome (NBCCS) is diagnosed in individuals with two major diagnostic criteria and one minor diagnostic criterion or one major and three minor diagnostic criteria [Evans et al 1993].

Although a typical facial gestalt is present in most individuals with NBCCS, measurement of head circumference and examination of the skin for basal cell carcinomas (BCCs), nevi, milia, and plantar/palmar pits is necessary for clinical diagnosis.

The availability of molecular genetic testing has broadened the phenotypic spectrum of NBCCS and, thus, individuals who do not fulfill all diagnostic criteria may be found to have pathogenic *PTCH* mutations. (An individual who is the first in the family to be affected may have milder signs because of somatic mosaicism.)

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. (Sella calcification, when present, is visible on lateral x-rays of the skull.)
- **Jaw keratocyst** (odontogenic keratocyst histologically; seen on orthopantogram as an area of translucency)
- **Palmar/plantar pits** (two or more); 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 BCCs** (more than five in a lifetime) or a BCC before age 30 years. Provision needs to be made for decreased risk of BCC in dark-skinned races and increased risk for Caucasians living in hot sunny climates.
- **First-degree relative with NBCCS**

Minor criteria

- Childhood medulloblastoma (also called primitive neuroectodermal tumor [PNET])
- 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*: bifid/splayed/extra ribs; bifid vertebrae
- Preaxial or postaxial polydactyly

- Ovarian/cardiac fibromas
- Ocular anomalies (cataract, developmental defects, and pigmentary changes of the retinal epithelium)

***Note about 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.

Note: (1) 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. (2) 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. (3) 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].

Testing

Cytogenetic analysis. Although chromosomal translocations or large cytogenetically detectable deletions on chromosome 9 have been reported in a small number of individuals with NBCCS, chromosome analysis is rarely likely to be helpful in diagnosis.

A 9q deletion should be considered when both of the following are present: clinical features consistent with NBCCS **and** additional features, including severe developmental delay or short stature. Presence of the latter features suggests that additional chromosomal material has been lost.

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Molecular Genetic Testing—Gene. *PTCH* is the only gene currently known to be associated with NBCCS.

Clinical testing

- **Sequence analysis** of exons 2-23 with intron-exon junctions and one of the splice forms of exon 1 detects mutations 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 *PTCH* mutation [Marsh et al 2005, Klein et al 2005].
- **Deletion testing** using any one of a variety of methods detects exonic and whole-gene deletions in 6% of individuals with NBCCS.

Table 1 summarizes molecular genetic testing for this disorder.

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

Test Method	Mutations Detected	Mutation Detection Frequency by Test Method [1]	Test Availability
Sequence analysis/ mutation scanning	*PTCH* sequence variants	50%-85%	Clinical Testing
Deletion testing [2]	*PTCH* exonic and whole-gene deletions	6%	

1. In individuals with typical clinical findings of NBCCS
2. By a variety of methods including MLPA (multiplex ligation-dependent probe amplification), real-time PCR (polymerase chain reaction), quantitative PCR

Interpretation of test results

- For issues to consider in interpretation of sequence analysis results, click here.
- Missense mutations are relatively common and may be difficult to interpret in an individual who has no family history of NBCCS and does not fulfill diagnostic criteria.
- The identification of a pathogenic mutation (nonsense, frameshift deletion/insertion, splice site) confirms a clinical diagnosis of NBCCS. Because some individuals with a clinical presentation consistent with NBCCS do not have *PTCH* mutations detectable by routine techniques, failure to detect a *PTCH* does not exclude the diagnosis of NBCCS.
- The sensitivity of the testing depends on both the test methods and the diagnostic criteria used. Low mutation detection rate in some studies may reflect the clinical diagnostic criteria rather than the molecular testing strategy [Boutet et al 2003].
- The likelihod of detecting a mutation may be lower in an individual who is known to be the first affected in the family, possibly because a *de novo* mutation has resulted in somatic mosaicism in that individual. In such cases, the likelihood of detecting a mutation is increased if the person tested is an affected child of an individual who has mild features of NBCCS.
- The same *PTCH* mutation present in two or more tumors but not present (or present at a lower-than-normal ratio) in lymphocyte DNA strongly suggests somatic mosaicism.

Testing Strategy

Confirmatory diagnostic testing. Molecular genetic testing can be used to confirm the diagnosis in individuals with atypical clinical findings.

Predictive testing for at-risk asymptomatic adult family members requires prior identification of the disease-causing mutation in the family.

Prenatal diagnosis and preimplantation genetic diagnosis (PGD) for at-risk pregnancies require prior identification of the disease-causing mutation in the family.

Genetically Related (Allelic) Disorders

Ming et al (2002) reported *PTCH* missense mutations in five of 100 unrelated probands with holoprosencephaly. The authors hypothesized that the missense mutations would lead to enhanced repressive activity of *PTCH* on the hedgehog signaling pathway, unlike the mechanism in NBCCS in which the pathway is activated, usually by haploinsufficiency for *PTCH*.

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

Clinical Description

Natural History

More than 100 features that are variable within and among families have been associated with nevoid basal cell carcinoma syndrome (NBCCS) [Farndon 2004].

Findings in their usual order of manifestation:

- **Appearance.** Approximately 60% of individuals with a *PTCH* mutation have a recognizable appearance with macrocephaly, bossing of the forehead, coarse facial features, and facial milia. The shoulders slope downward.
- **Macrocephaly.** The first feature likely to be observed is relative macrocephaly. A large proportion of babies with NBCCS require delivery by Caesarian 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.

  There is often some delay in motor milestones; most individuals catch up by about age five years. There is no published psychometric evidence for global delay.
- **Birth defects.** 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].

  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].
- **Medulloblastoma.** Approximately 5% of individuals with NBCCS develop the childhood brain malignancy medulloblastoma (now often called primitive neuroectodermal tumor [PNET]) [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 two years, compared to seven years in its sporadic form [Cowan et al 1997, Amlashi et al 2003].
- **Jaw keratocysts.** Approximately 90% of affected individuals 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.
- **BBCs.** 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 seem to be particularly radiosensitive, with new BCCs appearing in the field of radiation following radiotherapy.

Other skin manifestations. Other skin manifestations include facial milia, which can be numerous, and meibomian cysts in the eyelids. Sebaceous cysts and dermoid cysts are also common. 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 individuals [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 are usually an incidental finding on ultrasound examination or at Caesarian 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 of other malignant tumors is not clearly increased, although lymphoma and meningioma have been reported.

Morbidity/mortality. Life expectancy in NBCCS is not significantly different from average. 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.

Genotype-Phenotype Correlations

Early reports did not find a genotype-phenotype correlation [Wicking et al 1997]. Predictions about clinical severity are not yet possible for specific mutations, which are likely to be modified by the effects of other genes.

Some evidence is accumulating that *PTCH* missense mutations may be associated with a milder phenotype [P Farndon, unpublished data].

A large deletion has been identified in a family with an array of ophthalmic features, including a retinal pigmentary abnormality.

Penetrance

Although NBCCS shows intra- and interfamilial variation in expression, experience clinically and from molecular testing is compatible with complete penetrance.

Anticipation

No evidence of anticipation has been reported. Variable expressivity explains the instances in which children appear more severely affected than a parent.

Prevalence

Few studies of disease 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, Farndon et al 1991]. 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 1:40,000. The true figure may be even higher, as milder cases may not be recognized.

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

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

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 a typical facial appearance, intellectual impairment, and overgrowth (increased height and head circumference). It is associated with neonatal jaundice, scoliosis, seizures, strabismus, conductive hearing loss, congenital cardiac anomalies, renal anomalies, and behavioral problems. The risk of sacrococcygeal teratoma and neuroblastoma is slightly increased. Approximately 80%-90% of individuals with Sotos syndrome have a demonstrable mutation or deletion of NSD1. Sotos syndrome is inherited in an autosomal dominant manner, with more than 95% of individuals having a *de novo* mutation.
- **Beckwith-Wiedemann syndrome** is a disorder of growth characterized by macrosomia (large body size), macroglossia, visceromegaly, embryonal tumors (e.g., Wilms tumor, hepatoblastoma, neuroblastoma, rhabdomyosarcoma), omphalocele, neonatal hypoglycemia, ear creases/pits, adrenocortical cytomegaly, and renal abnormalities (e.g., medullary dysplasia, nephrocalcinosis, medullary sponge kidney, and nephromegaly). 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. The diagnosis relies primarily on clinical findings, but molecular genetic testing reveals diagnostic changes in some affected individuals.
- **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:

- Trichoepitheliomas, milia, and cylindromas presenting in the second or third decade 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 dominant.

- Rombo syndrome, a dominantly inherited condition similiar 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 dominant syndrome of hypotrichosis and BCCs reported in a single family [Oley et al 1992] (see 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.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with nevoid basal cell carcinoma syndrome (NBCCS), the following evaluations are recommended:

- Baseline measurement of head circumference, preferably with plotting 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 clefting, polydactyly)
- X-rays to evaluate for rib and vertebral anomalies and falx calcification
- 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
- Ophthalmologic evaluation for evidence of cataract, developmental defects, and pigmentary changes of the retinal epithelium
- 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

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, medical geneticist) experienced with the condition.

Keratocysts identified early in life usually need 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. 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.

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

Sun exposure and x-irradiation should be avoided.

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 computer tomography (CT) should be avoided because of risks associated with radiation sensitivity.

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.

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

Agents/Circumstances to Avoid

Excessive sun exposure increases the likelihood of developing BCCs. Affected individuals should use complete sunblock and cover the skin by wearing long sleeves, high collars and hats.

Use of radiotherapy can lead to the development of thousands of BCCs in the radiation field [Strong 1977; Evans, Birch et al 1991] and is not recommended. If the treating team believes that no other treatment modality is possible, radiotherapy should be used through as few skin ports as possible.

Testing of Relatives at Risk

Because of the need for surveillance for complications of NBCCS (most notably medulloblastoma in children and jaw cysts and BCCs in adults) and the need for sun screening, clarification of the genetic status of at-risk relatives, including children, is appropriate.

- Molecular genetic testing is possible if a pathogenic mutation has been identified in an affected family member.
- 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 features of NBCCS.

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

Therapies Under Investigation

Photodynamic therapy (with infra-red light) is showing early promise and appears safe [Haylett et al 2003]

Aminolevulinic acid has been investigated [Itkin & Gilchrist 2004, Oseroff et al 2005]

Topical treatment with 5 fluorouracil (Efudex®) or imiquimod (5%) is under investigation [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.

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Other

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

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. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

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.
- Approximately 20%-30% of probands have a *de novo* mutation.

- Recommendations for the evaluation of parents of a proband with an apparent *de novo* mutation 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 *PTCH* mutation has been identified in the proband or other affected family member.

Note: (1) Although 70%-80% of individuals diagnosed with NBCCS have an affected parent, the family history may appear to be negative as a result of failure to recognize the disorder in family members because of variable expressivity. (2) If the parent is the individual in whom the mutation first occurred, s/he may have somatic mosaicism for the mutation, and may be mildly/minimally affected.

Sibs of a proband

- The risk to a sib depends on the genetic status of the 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 disease-causing mutation cannot be detected in the DNA of the parent, the risk to sibs is low, but greater than that of the general population because of the possibility of somatic mosaicism or germline mosaicism.

Offspring of a proband

- Each child of an affected individual has a 50% risk of inheriting the mutation.
- The offspring of an individual with mild NBCCS caused by somatic mosaicism may be at less than a 50% risk of inheriting the disease-causing mutation.

Other family members

- The risk to other family members depends on the genetic status of the proband's parents.
- If a parent is found to be affected, his or her family members are at risk.

Related Genetic Counseling Issues

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:

- Genetic Cancer Risk Assessment and Counseling: Recommendations of the National Society of Genetic Counselors
- Elements of Cancer Genetics Risk Assessment and Counseling (part of PDQ®, National Cancer Institute)

Considerations in families with an apparent *de novo* mutation. When neither parent of a proband with an autosomal dominant condition has the disease-causing mutation or clinical evidence of the disorder, it is likely that the proband has a *de novo* mutation. However, possible non-medical explanations including alternate paternity or undisclosed adoption could also be explored.

Family planning. The optimal time for determination of genetic risk and discussion of the availability of prenatal testing is before pregnancy. Similarly, decisions about testing to

determine the genetic status of at-risk asymptomatic family members are best made before pregnancy.

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 features of NBCCS. Molecular genetic testing may be considered if a pathogenic mutation 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 *PTCH*.

DNA banking. 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, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant when the sensitivity of currently available testing is less than 100%. See Testing for a list of laboratories offering DNA banking.

Prenatal Testing

Prenatal diagnosis for pregnancies at increased risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at approximately 15-18 weeks' gestation or chorionic villus sampling (CVS) at approximately ten to 12 weeks' gestation. The disease-causing allele of an affected family member must be identified before prenatal testing can be performed.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Requests for prenatal testing for conditions such as NBCCS that do not affect intellect, have variable expression, and have some treatment available are not common. Differences in perspective may exist among medical professionals and in families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. Although most centers would consider decisions about prenatal testing to be the choice of the parents, discussion of these issues is appropriate.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutation has been identified. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A .Molecular Genetics of Nevoid Basal Cell Carcinoma Syndrome

Gene Symbol	Chromosomal Locus	Protein Name
PTCH1	9q22.3	Protein patched homolog 1

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Nevoid Basal Cell Carcinoma Syndrome

109400	BASAL CELL NEVUS SYNDROME; BCNS
601309	PATCHED, DROSOPHILA, HOMOLOG OF, 1; PTCH1

Table C. Genomic Databases for Nevoid Basal Cell Carcinoma Syndrome

Gene Symbol	Locus Specific	Entrez Gene	HGMD
PTCH1	PTCH1	5727 (MIM No. 601309)	PTCH

For a description of the genomic databases listed, click here.

Note: HGMD requires registration.

Molecular Genetic Pathogenesis

The comparatively young mean age at onset of medulloblastoma in individuals with nevoid basal cell carcinoma syndrome (NBCCS) (two years, versus seven years in the general population) and the loss of the normal copy of the gene in tumors [Cowan et al 1997] confirm *PTCH* as a tumor suppressor in medulloblastoma as well as in BCC. Inactivation of the normal gene 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].

PTCH2, highly homologous to *PTCH*, was mapped to chromosome 1p32.1-p32.3 [Smyth et al 1999]. Mutations were found in one simplex case (i.e., a single occurrence of the disease in a family) of medulloblastoma and one simplex case of BCC. No *PTCH2* mutations were found in 11 simplex cases of NBCCS or 11 individuals with familial cases of NBCCS who did not have identifiable *PTCH* mutations.

Normal allelic variants: The *PTCH* gene consists of 23 exons. Polymorphisms in *PTCH* have been identified. Information is being collected about possible effects on the function of the protein.

Pathologic allelic variants: See Table 3.

Table 3. Frequency of Pathogenic Genetic Mechanisms

% of Individuals [1]	Type of Mutation
65%	Truncating
16%	Missense
13%	Splice-site
6%	Intragenic or large scale deletions or rearrangements

1. Source: literature and 395 samples from diagnostic laboratory, Birmingham Women's Hospital, UK, August 2007 (Proportions of types of mutation have remained the same over several years.)

Normal gene product: 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 coreceptor smoothened (SMOH). 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].

Abnormal gene product: Pathologic variants found in individuals with NBCCS and nonfamilial BCC include those predicted to result in a truncated protein and missense mutations.

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

BCCNS Life Support Network
PO Box 321
Burton OH 44021
Phone: 866-834-1895; 440-635-0078
Email: info@bccns.org
www.bccns.org

Gorlin Syndrome Group
Phone: +44 (0) 1772 517624 (helpline)
Email: info@gorlingroup.co.uk
www.gorlingroup.co.uk

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

American Society of Clinical Oncology (2003) Statement on genetic testing for cancer susceptibility

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Chapter Notes

Author Notes

Professor Evans coordinates the cancer genetic services for the Northwest Region population of England (4.3 million), 4-5 clinics per week with outreach clinics, and is laboratory liaison for cancer genetic testing (BRCA1/2, TP53, NF1, NF2, Gorlin syndrome, APC, MEN1/2, vHL). Professor Evans has published over 300 papers, 30 book chapters, and a book on hereditary cancer. He is an active clinical researcher in cancer predisposition syndromes.

Professor Farndon holds genetic clinics in the West Midlands Region and a special clinic for patients with Gorlin syndrome. He is a medical advisor to the UK Gorlin Syndrome support group. Professor Farndon performed the first population study of Gorlin syndrome and his was one of the groups that mapped the gene. He is medical advisor to the Birmingham NHS laboratory providing clinical *PTCH* molecular genetic testing. His current research includes genotype-phenotype correlation, especially involving the other genes in the HH-PTCH pathway.

Revision History

- 25 January 2008 (me) Comprehensive update posted to live Web site
- 6 October 2004 (me) Comprehensive update posted to live Web site

- 20 June 2002 (me) Review posted to live Web site
- 21 November 2001 (pf) Original submission