

Clinical and genetic findings in 103 individuals in Norway with basal cell naevus syndrome

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Abstract

Background Basal cell naevus syndrome (BCNS) is a rare autosomal dominant condition characterized by early onset and multiple basal cell carcinomas (BCCs), skeletal and ocular abnormalities, and extracutaneous tumours and cysts. In most cases, BCNS is caused by a pathogenic variant in the tumour suppressor gene *PTCH1*. Pathogenic variants in *SUFU* account for a minority of cases. No clear genotype–phenotype associations between different *PTCH1* variants have been established.

Objectives To identify all individuals with BCNS in Norway, characterize their clinical and genetic profiles, and investigate possible genotype–phenotype associations.

Methods In this cross-sectional study, we approached all individuals with BCNS registered at the Department of Dermatology at Oslo University Hospital and two national resource centres for rare medical conditions. Dermatologists, dentists and geneticists across Norway were contacted in order to identify additional individuals with BCNS. Data were collected from structured interviews, whole-body physical examinations, electronic medical records, radiographic imaging and molecular genetic analyses.

Results We identified 109 individuals with BCNS, indicating a national prevalence of BCNS of at least 1.9 per 100 000, of whom 103 agreed to be included. Clinical findings confirmed the considerable phenotypic variation in BCNS, including BCC in 61 individuals (median number of BCCs 48, range 1–1025), odontogenic keratocysts in 72 (median number of odontogenic keratocysts 5, range 1–30) and a wide spectrum of ocular and skeletal abnormalities in 43 and 98 individuals, respectively. This study is the first to report the prevalence estimates of autism (4%) and epilepsy (7%), as well as intracranial lesions associated with epilepsy, in BCNS. Genetic analyses identified a pathogenic or probable pathogenic *PTCH1* variant in 93 individuals, while 5 individuals had variants of uncertain clinical significance. Twenty-one of the pathogenic *PTCH1* variants were novel. None of the individuals with *PTCH1* variants in exon 1, all belonging to the same family, exhibited BCCs, odontogenic keratocysts or palmoplantar pitting.

Conclusions This study expands the number of pathogenic *PTCH1* variants, elucidates important clinical aspects in BCNS and reveals novel insight to genotype–phenotype associations, providing new implications for management and follow-up.

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Lay summary

Basal cell naevus syndrome, or 'BCNS' for short, is a rare genetic condition. It affects about 2 in every 100,000 individuals. It is also known as 'Gorlin syndrome'. From a young age, individuals with the condition often develop a particular type of skin cancer called 'BCC'. Many individuals with the condition can also experience jaw cysts and other health issues. Changes in a gene called 'PTCH1' cause most cases of the condition. But, how different genetic changes influence the health issues experienced by individuals with BCNS is not well understood.

We aimed to find all individuals in Norway with the condition and describe their health and genetic backgrounds. To gather this information, we carried out interviews and physical examinations, and collected information from medical records, X-rays and genetic analyses.

We identified 109 individuals with BCNS across Norway. Of these individuals, 103 agreed to take part in the study. Nearly all had a change in the PTCH1 gene. Twenty-one of the genetic changes had not been found before. Individuals with the condition experienced a variety of health issues. These included BCC, jaw cysts, eye problems and skeletal abnormalities. More individuals with the condition experienced epilepsy and autism than individuals in the general population of Norway. We also found a relationship between epilepsy and areas of abnormal brain tissue in individuals with the condition. Individuals with changes in a part of the PTCH1 gene called 'exon 1' had milder health issues than others.

Our study provides new insights into the physical and genetic issues experienced in individuals with BCNS. Based on this, new ways to guide future care and monitoring are discussed.

What is already known about this topic?

- Basal cell naevus syndrome (BCNS) is a rare autosomal dominant condition characterized by early onset and multiple basal cell carcinomas, skeletal and ocular abnormalities, and extracutaneous tumours and cysts.
- In most cases, BCNS is caused by pathogenic variants in the *PTCH1* gene.
- The BCNS phenotype varies considerably and no clear genotype–phenotype associations between different types of pathogenic *PTCH1* variants have been established.

What does this study add?

- This study characterizes one of the largest cohorts of individuals with BCNS to date and identifies 21 novel pathogenic *PTCH1* variants.
- The study elucidates important clinical aspects in BCNS, including the first prevalence estimates of autism (4%) and epilepsy (7%), providing new implications for management and follow-up.
- New genotype–phenotype associations in BCNS are revealed, highlighting a milder phenotype for individuals with *PTCH1* variants located in exon 1.

Basal cell naevus syndrome (BCNS; OMIM #109400), also known as naevoid basal cell carcinoma syndrome and Gorlin syndrome, is a rare autosomal dominant condition characterized by multiple basal cell carcinomas (BCCs) from a young age. The clinical presentation of BCNS is highly variable, with additional common features including odontogenic keratocysts, palmoplantar pitting, skeletal and ocular abnormalities, and extracutaneous tumours.¹ Different diagnostic criteria for BCNS have been suggested,^{2–4} revisited by Bree and Shah in 2011 (Table 1).⁵

BCNS is most commonly caused by a heterozygote germline pathogenic variant in the tumour suppressor gene *PTCH1* on chromosome 9q22.31,^{6–9} a gene involved in the Hedgehog signalling pathway.¹⁰ Pathogenic variants in *SUFU*, another gene involved in the same signalling pathway, account for a minority of cases.^{11,12}

Only a few large cohorts of individuals with BCNS have been published.^{3,4,13–16} Evidence suggests some genotype–phenotype differences between *PTCH1* and *SUFU* pathogenic variants in BCNS.^{11,17} In contrast, no clear genotype–phenotype associations between different *PTCH1* variants have been established.^{15–18} We aimed

to identify and characterize all individuals in Norway with BCNS, and to explore novel clinical aspects, gene variants and genotype–phenotype associations.

Materials and methods

Study design

We set up a nationwide cross-sectional study of all identified individuals in Norway with BCNS. Two individuals with BCNS contributed to the study planning and emphasized aspects important to this patient group. We conducted the study in accordance with the STROBE statement.¹⁹

Study population

From August 2021 to July 2024 we approached all individuals with a confirmed diagnosis of BCNS registered at the Department of Dermatology and the Resource Centre for Rare Disorders at Oslo University Hospital and the Norwegian National Resource Centre for Oral Health in Rare Disorders

Table 1 Diagnostic criteria for basal cell naevus syndrome (BCNS),^a as outlined by Bree and Shah⁵

Major criteria	Minor criteria
BCCs before the age of 20 years or excessive number of BCCs out of proportion to prior sun exposure and skin type	Rib anomalies
Odontogenic keratocysts of the jaw before the age of 20 years	Other specific skeletal malformations and radiological changes (i.e. vertebral anomalies, kyphoscoliosis, short fourth metacarpals and postaxial polydactyly)
Palmar or plantar pitting	Macrocephaly
Calcification of the falx cerebri	Cleft lip/palate
Medulloblastoma, typically desmoplastic variant	Ovarian/cardiac fibroma
First-degree relative with BCNS	Lymphomesenteric cysts
	Ocular abnormalities (i.e. strabismus, hypertelorism, congenital cataracts, glaucoma and coloboma)

BCC, basal cell carcinoma. ^aDiagnosis is based on (i) one major criterion and molecular confirmation; (ii) two major criteria; or (iii) one major and two minor criteria.

at Lovisenberg Diaconal Hospital, Oslo. Additionally, we contacted dermatologists, dentists and geneticists in all health regions in Norway, and posted information about the study on the national BCNS Facebook group and the BCNS page of the Oslo University Hospital's website. All identified individuals with BCNS were invited to participate in a multidisciplinary evaluation and to be included in the Oslo University Hospital Skin Registry – Dermareg, a consent-based quality and research registry.

Data collection

Structured interviews covering a detailed history of somatic and mental health, and family history, were conducted with all individuals ($n=103$). A whole-body physical examination was performed of those attending onsite ($n=90$). The interviews and examinations were conducted by two dermatologists with specialized expertise in BCNS (K.H.B. and K.H.H.), in collaboration with relevant specialists from the multidisciplinary BCNS team. Additionally, data were collected retrospectively from electronic medical records, radiographs and molecular genetic analyses. Existing radiographs were re-examined by one radiologist. We avoided any additional radiological examinations if they were not deemed to be therapeutically beneficial.

In individuals without a known family history of BCNS, *PTCH1* was initially analysed using next-generation sequencing with copy number variation analysis, multiplex ligation-dependent probe amplification and/or Sanger sequencing. If no pathogenic variant was identified, additional analyses for *SUFU*, *PTCH2* and *SMO* were conducted. In families with a known pathogenic variant, targeted Sanger sequencing was performed for that specific variant. Genetic analyses were reclassified according to American College of Medical Genetics and Genomics standards and guidelines,²⁰ and Association for Clinical Genomic Science standards and guidelines.²¹

Statistical analyses

Statistical analyses were done using Stata software version 18 (StataCorp, Cary, NC, USA) and with an alpha level of 0.05. For normally distributed variables, we report the mean. For non-normally distributed variables, we report the median. The distribution of the onset of the first BCC and the first odontogenic keratocyst was estimated by

Kaplan–Meier analysis. Univariate linear regressions were performed for continuous variables (i.e. age at first BCC) and logistic regressions for dichotomous variables (i.e. ≥ 10 BCCs, ≥ 20 BCCs and ≥ 10 odontogenic keratocysts). Tests according to genotypes were adjusted for clusters of families. Genotype–phenotype associations were investigated further by constructing heat maps. For comparison of our BCNS cohort with the Norwegian population,^{22–25} one-sample *t*-tests were used for means and one-sample proportion *z*-tests for proportions.

Results

We identified 109 individuals in Norway with BCNS, corresponding to a national BCNS prevalence of 1.9 : 100 000. The estimated prevalence varied between the four geographical health regions, ranging from 0.4 : 100 000 in the northern region to 3.4 : 100 000 in the western region (Table S1; see [Supporting Information](#)). Six individuals did not consent to participate in the study, establishing a BCNS cohort

Table 2 Demographic and clinical characteristics of 103 individuals in Norway with basal cell naevus syndrome

Characteristic	<i>n</i> (%)
Age (years), mean (SD)	35 (22)
Median (range)	31 (1–78)
Sex	
Female	50 (49)
Male	53 (51)
Fitzpatrick skin phototype	
I	11 (11)
II	74 (72)
III	8 (8)
IV	2 (2)
V	0
VI	0
Unknown	8 (8)
Age at diagnosis (years), mean (SD)	20 (17)
Median (range)	15 (0–74)
Age at first diagnosed BCC (years), mean (SD)	30 (12)
Median (range)	30 (5–55)
Age at first odontogenic keratocyst removal (years), mean (SD)	16 (9)
Median (range)	13 (6–47)

Data are presented as *n* (%) unless otherwise stated. BCC, basal cell carcinoma.

Table 3 Clinical manifestations in 103 individuals in Norway with basal cell naevus syndrome

Manifestations	n
Cutaneous	
Palmar and/or plantar pitting	73
≥ 1 BCC	61
Milia	18
Benign cysts	9
Chalazion	7
Hair patches	3
Café-au-lait patches	2
Multiple melanocyte naevi	1
Ocular	
Strabismus	26
Severe refraction error ^a	9
Myelinated optic nerve fibre layers	6
Epiretinal membranes	6
Congenital/juvenile cataract	4
Amblyopia	3
Corneal dystrophy	2
Congenital/juvenile glaucoma	2
Anisometropia	2
Benign tumour	2
Ptosis	1
Microphthalmia	1
Skeletal	
Frontoparietal bossing	77
Macrocephaly	75
Broad nasal bridge	68
Scoliosis/kyphosis	23
Pectus deformity/thorax abnormality	19
Rib abnormality	18
Vertebral abnormality	17
Foot abnormality ^b	13
Prognathism	11
Cleft lip/palate	8
Sloping, narrow shoulders	6
Craniosynostosis	5
Sprengel deformity	3
Syndactyly ^c	3
Polydactyly ^d	3
Anisomelia	2
Postaxial synpolydactyly	1
Brachydactyly	1
Thumb abnormality, not further classified	1
Nervous system	
Calcification of falx cerebri	30
Hydrocephalus	12
Intracranial tumour ^e	7
Epilepsy	7
Intracranial cysts	3
Chiari malformation	2
Ganglion cyst	2
Plantar neuroma	1
Stomatognathic system	
Odontogenic keratocysts	72
Cardiovascular system	
Stroke	6
Cardiac fibroma	4
Genitourinary	
Cryptorchidism	4
Ovarian fibroma	3
Myoma uteri	3
Ovarian cysts	2
Simple kidney cyst	1
Unilateral renal agenesis	1
Gastrointestinal	
Lymphomesenteric cysts	3
Pancreatic cyst	1
Liver cyst	1
Oesophageal leiomyoma	1

(Continued)

Table 3 (Continued)

Manifestations	n
Congenital pylorus stenosis	1
Other benign tumours and cysts	
Dermoid cyst	3
Lipoma	2
Leiomyoma of the hand	1
Papillary cystadenoma lymphomatosum	1
Lateral cyst of the neck	1
Developmental and mental difficulties	
Depression	15
Anxiety	10
Intellectual disability	7
ADHD	6
Autism	4
Alcohol and/or drug abuse	2
Eating disorder	1

ADHD, attention deficit/hyperactivity disorder; BCC, basal cell carcinoma. ^aDefined as myopia ≥ 6.00 D, hypermetropia ≥ 5.00 D, and/or astigmatism (cylinder) ≥ 3.00 D. ^bIncluding pes planus (*n* = 5), coalition (*n* = 4), pes planovalgus (*n* = 3), pes calcaneovalgus (*n* = 1) and pes equino varus (*n* = 1). One individual had coalition and pes calcaneovalgus. ^cIncluding syndactyly of fingers (*n* = 1) and syndactyly of toes (*n* = 2). ^dIncluding preaxial polydactyly (*n* = 1), postaxial polydactyly (*n* = 1) and polydactyly not further specified (*n* = 1). ^eIncluding medulloblastoma (*n* = 1), meningioma (*n* = 4), tectal glioma (*n* = 1), intracranial lipomatous tumour (*n* = 1) and pituitary microadenoma (*n* = 1). One individual presented with both a meningioma and a pituitary microadenoma.

of 103 individuals. The demographic characteristics of the participants and the clinical manifestations are presented in detail in Tables 2 and 3, respectively.

Cutaneous manifestations

Age at first BCC diagnosis varied considerably (Figure 1). The median number of diagnosed BCCs was 48 (range 1–1025). Of the 61 individuals diagnosed with BCCs, 53 (87%) had at least 5 diagnosed BCCs and 23 (38%) had ≥ 100 BCCs diagnosed. Nodular BCC was the most frequent BCC subtype (in 53 individuals) followed by superficial BCC (in 50 individuals) and infiltrative BCC (in 31 individuals). No melanoma and no squamous cell carcinoma other than one keratoacanthoma was registered. Twenty individuals presented with multiple pigmented or skin-coloured papules with dermatoscopic features excluding melanocyte naevi and without convincing features of a nodular, superficial or infiltrative BCC.

Stomatognathic manifestations

Age at diagnosis of first odontogenic keratocyst varied (Figure 1), with the median age being 13 years (range 6–47). The median number of removed odontogenic keratocysts was 5 (range 1–30). Among individuals aged ≥ 20 years, 25 of 26 individuals (96%) diagnosed with BCNS before the age of 20 years underwent keratocyst removal before they were 20 years old. Of 44 individuals diagnosed with BCNS after the age of 20 years, 12 had not developed any keratocysts, while 14 had their first keratocyst removed after they reached 20 years of age. None of these 14 individuals was screened for keratocysts prior to age 20 years.

Ocular manifestations

Ocular abnormalities encompassing a wide spectrum were identified in 43 of 103 individuals (42%); multiple findings

were found in 10 of them (Table 3). The two ocular tumours comprised a retinal hamartoma and a tumour of unknown type. A broad nasal bridge was present in 24 of the 26 individuals (92%) with strabismus.

Skeletal manifestations

The mean height of individuals aged ≥ 18 years was significantly higher than that of the general population of Norway: 7 cm higher in women (174 cm vs. 167 cm, $P < 0.001$) and 6 cm in men (187 cm vs. 181 cm; $P < 0.001$). Ninety-eight individuals (95%) presented with at least 1 skeletal abnormality (Table 3), including 46 individuals with ≥ 4 abnormalities. Eighteen individuals (17%) had hand and/or foot deformities.

Manifestations in the nervous system

Seven individuals were registered as having intracranial tumours (Table 3). The rate of epilepsy in those with BCNS was 7% vs. 0.7–0.8% in the general population of Norway ($P < 0.001$). Among those with epilepsy, two had intracranial tumours and one had an intracranial cyst. Hydrocephalus was registered in 12 individuals, with prior shunt surgery in 8 of them. Six individuals had experienced stroke, including one newborn baby and one 48-year-old at the time of stroke. None of the individuals with stroke had a cardiac fibroma.

Manifestations in other organs

A wide spectrum of benign tumours and cysts in several organ systems was identified (Table 3). Four individuals had extracutaneous malignancies: colorectal cancer, larynx cancer, B-cell lymphoma and rhabdomyosarcoma.

Developmental and psychiatric difficulties

The rate of autism in those with BCNS was 4% vs. 0.6% in the general population of Norway ($P < 0.001$). Intellectual

disability was registered in seven individuals, including one born prematurely at 24 weeks, one with neonatal meningitis and one with a duplication of 500 kB at chromosome 15q13, including *CHRNA7*, alongside a pathogenic *PTCH1* variant. Up to the time of inclusion, 15 of 72 (21%) individuals aged ≥ 18 years reported symptoms of depression and 9 (13%) reported anxiety.

Genetics

Ninety-nine individuals (96%) underwent molecular genetic testing. A pathogenic (class 5) or probable pathogenic (class 4) variant in *PTCH1* was identified in 93 individuals (94%) (Table S2; see [Supporting Information](#)). Five individuals had variants of uncertain clinical significance (class 3+), all of whom fulfilled the clinical diagnostic criteria for BCNS. The four untested individuals belonged to families with a known pathogenic *PTCH1* variant and fulfilled the clinical diagnostic criteria for BCNS. Most of the variants were loss-of-function variants (nonsense, frameshift, splice site or copy number variants). Only seven variants were missense. Twenty-one of the *PTCH1* variants have not been published previously (Table 4). The pathogenic *PTCH1* variants were inherited in 56 individuals and arose *de novo* in 36. The identified *PTCH1* variants were exclusive for each family (Table 4), except in two families.

Genotype–phenotype associations

The heat map sorted after locating the pathogenic variants in *PTCH1* showed that none of the five individuals with variants in exon 1 (median age 38 years, range 1–69) exhibited BCCs, odontogenic keratocysts or palmo-plantar pitting (Figure S1; see [Supporting Information](#)). All of these individuals belonged to the same family, one of whom fulfilled the diagnostic criteria for BCNS independent of molecular analysis and a first-degree relative with BCNS. All family members harboured the same class 5 (pathogenic) variant (c.113_114delinsC). No additional clustering of clinical features by *PTCH1* variant location or variant type was seen in the heat maps.

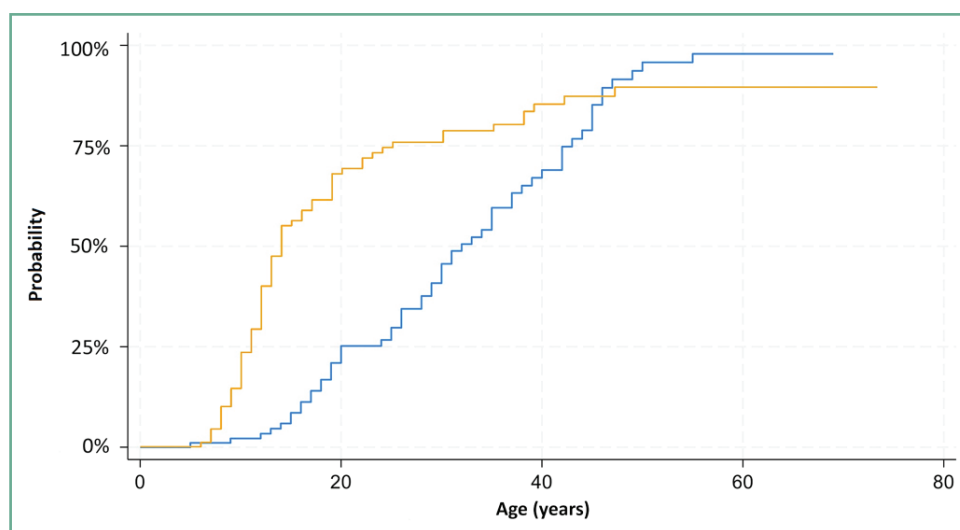


Figure 1 Cumulative onset of basal cell carcinomas (blue line) and odontogenic keratocysts (orange line) in 103 individuals with basal cell naevus syndrome in Norway.

Table 4 Novel *PTCH1* variants in individuals in Norway with basal cell naevus syndrome

DNA and predicted protein change	Type variant	Classification of pathogenicity ^a
c.113_114delinsC, p.(Gly38Alafs*42)	Frameshift	5
c.230dup, p.(Trp78Valfs*12)	Frameshift	5
c.411del, p.(Arg138Valfs*3)	Frameshift	5
c.608_609del, p.(Cys203Leufs*48)	Frameshift	5
c.654G>A, r.585_654del, p.(Gln196*)	Splice site	5
c.734del, p.(Thr245Lysfs*5)	Frameshift	5
c.746+1G>A, p.(?)	Splice site	5
c.934_935del, p.(Asn312Phefs*6)	Frameshift	5
c.1208dup, p.(Tyr403*)	Frameshift	5
c.1350_1354dup, p.(Tyr452Serfs*6)	Frameshift	5
c.1537G>C, p.(Asp513His)	Missense	4
c.1759del, p.(Met587Trpfs*36)	Frameshift	5
c.1847+2T>C, p.(?)	Splice site	5
c.2025C>G, p.(Tyr675*)	Nonsense	5
c.2405_2412delinsC, p.(Asn802Thrfs*2)	Frameshift	5
c.2577del, p.(Phe859Leufs*44)	Frameshift	5
c.2829del, p.(His944Thrfs*18)	Frameshift	5
c.2887_2887+1dup, p.(Ile963Lysfs*33)	Frameshift	5
c.3081G>A, p.(Trp1027*)	Nonsense	5
c.3106_3108del, p.(Leu1036del)	Inframe deletion	4
c.3296del, p.(His1099Profs*7)	Frameshift	5

Variants are listed according to location in the gene (i.e. from start to end). Reference sequence used: NM_000264.5. ^aClass 4 and 5 are likely to be pathogenic and pathogenic variants, respectively.

There were no significant differences in age at diagnosis of the first BCC in individuals with *PTCH1* missense variants compared with those with other *PTCH1* variants. There were also no significant differences in the likelihood of ≥ 10 BCCs, ≥ 20 BCCs or ≥ 10 odontogenic keratocysts.

Discussion

We present one of the largest and most comprehensively characterized cohorts of individuals with BCNS reported worldwide. The study reports 21 previously unpublished *PTCH1* variants, presents novel insights into genotype–phenotype associations in BCNS and reveals important clinical aspects with implications for the management and follow-up of BCNS.

The 21 novel *PTCH1* variants reported expands the spectrum of identified pathogenic variants in BCNS. All observed *PTCH1* variants were unique for each family, with one exception. This supports BCNS being linked to a wide range of pathogenic *PTCH1* variants and with a high rate of private pathogenic variants.¹⁸ We did not find any cases of BCNS caused by pathogenic *SUFU* variants, which is possibly explained by under ascertainment due to the less prominent BCNS features in individuals with these variants.²⁶

Heat maps revealed a pathogenic *PTCH1* variant in exon 1 where none of the affected family members had developed BCCs, odontogenic keratocysts or palmoplantar pitting. To our knowledge, only two case reports of individuals with

pathogenic *PTCH1* variants in exon 1 have previously been published,^{27,28} one of whom was a 9-year-old boy without BCC, odontogenic keratocysts or palmoplantar pits. The other, a 27-year-old male, had no BCCs but did have odontogenic keratocysts and palmoplantar pits. These findings suggest that individuals with pathogenic *PTCH1* variants in exon 1 do not develop BCCs. However, due to the limited number of individuals, some of whom are young, no firm conclusions should be drawn. The mechanism resulting in the milder phenotype in those with exon 1 pathogenic variants is not well understood, but use of alternative first exons could possibly explain the milder phenotype observed.^{28,29} Further studies are needed to clarify this.

Despite achieving a high level of detail in genetic and clinical data for the 103 individuals included in this study, we could not confirm the previously suggested milder phenotype in individuals with missense *PTCH1* variants.^{16,17} This could be due to a limited number of individuals with missense variants. In addition to increasing the number of individuals in future studies, the use of novel genetic methods could be considered to elucidate epigenetic modifications and other gene regulatory mechanisms in BCNS.

Cutaneous findings revealed the highest mean age at diagnosis of first BCC in a cohort predominantly consisting of White European individuals.^{15,30–32} The northern latitudes, which experience less ultraviolet radiation, may contribute to later development of the first BCC. Nevertheless, many individuals in this study were diagnosed with BCC during childhood and adolescence, nearly all individuals aged ≥ 60 years were diagnosed with BCCs and more than one-third had ≥ 100 BCCs diagnosed. This underscores the importance of regular dermatological examination from an early age, even at northern latitudes.

Importantly, we found no cases of melanoma or squamous cell carcinoma, except one case of keratoacanthoma. These findings indicate that individuals with BCNS do not have an increased risk of skin cancers other than BCC. This contrasts with a previous study, where individuals with BCNS reported high rates of skin cancers other than BCC.¹⁵ We did not find an increased rate of multiple melanocyte naevi, indicating that this manifestation is not related to BCNS, as suggested previously.³³ However, 20 individuals had multiple pigmented or skin-coloured papules. The nature of these lesions is not well understood, but it has been suggested that they may represent a subtype of BCC or basaloid follicular hamartomas.³⁴ Further studies are warranted for clarification of this.

To our knowledge, we are the first to report the prevalence of hair patches in BCNS, a manifestation previously only mentioned in case reports.^{35–37} Recognizing this feature can help with an early diagnosis of BCNS.

Nearly all individuals diagnosed with BCNS in childhood or adolescence had their first odontogenic keratocyst removal before they were 20 years old. Among those whose first cyst removal occurred after the age of 20 years, none had been screened before 20 years of age, as their BCNS diagnosis was made in adulthood. This suggests that odontogenic keratocysts develop before 20 years of age, supporting regular surveillance from childhood.¹

Nearly half of the individuals included in our study had at least one ocular abnormality, which were either congenital or presented during childhood. Importantly, many of these

abnormalities require early treatment to prevent permanent visual loss. Therefore, we suggest a routine ophthalmological examination every second year up to the age of 12 years, in addition to the baseline examination recommended in existing guidelines.¹

To our knowledge this is the first report of an association between strabismus and a broad nasal bridge in BCNS. We hypothesize that a broad nasal bridge may predispose to strabismus in BCNS. However, some cases recorded as strabismus may represent pseudostrabismus rather than true ocular misalignment.³⁸ Further studies are needed to explore this relationship further.

We found that men and women with BCNS were significantly taller compared with the general population of Norway. The awareness of increased height as a manifestation of BCNS may contribute to an earlier diagnosis.

We avoided additional radiological examinations when it had no therapeutic consequence, in accordance with existing guidelines.¹ This probably explains the lower rates of rib and vertebral abnormalities, as well as calcification of falx cerebri, than reported in previous studies.^{4,13} Skeletal abnormalities can contribute to a BCNS diagnosis and some require treatment. Therefore, we recommend an assessment by an orthopaedic surgeon at the time of diagnosis, with follow-up depending on symptoms, complementing current guidelines.¹

To our knowledge, we are the first to report the prevalence of autism (4%) and epilepsy (7%) in BCNS, indicating that these may be relatively common features of BCNS. Clinicians should be aware of autism and epilepsy in the management of BCNS, and parents should be informed of the risks and associated symptoms.

We found a wide range of benign tumours and cysts, suggesting they are manifestations of BCNS. Importantly, we found a high rate of intracranial tumours and cysts, and an association between epilepsy and intracranial lesions, in BCNS. However, the rate of medulloblastoma was low (1%), probably due to the absence of individuals with *SUFU* variants. As many had intracranial lesions, we suggest a magnetic resonance imaging of the brain in individuals with BCNS presenting with cerebral symptoms, regardless of their age or pathogenic variant type, complementing existing guidelines.^{1,39}

Seven individuals were registered as having ID, although causes other than BCNS may have contributed to this. ID in BCNS has previously been reported in case reports and cohort studies.^{13,32,40–44} However, structured genetic testing for causes beyond BCNS is lacking in most of these reports. Further studies are needed to conclude whether ID should be considered a manifestation of BCNS.

We found high rates of self-reported symptoms of depression and anxiety, in line with a recent survey.³⁹ This warrants attention being paid to psychological distress and the need for further studies to assess individuals' quality of life.

Our estimated prevalence of BCNS in Norway falls within the range seen in other countries.^{45,46} Prevalence varied somewhat across the four geographical regions of Norway, with the northern region exhibiting the lowest rate of BCNS. The reason for this variation is unclear, but reduced ultraviolet radiation, especially in the north, may hinder the identification of BCNS in individuals with few BCCs. Additionally, BCNS is a rare condition with a significant proportion of *de*

novo variants and highly variable expressivity. Recognizing individuals with milder phenotypes, especially *de novo* cases, may be challenging. The lower number of individuals included from the northern region, combined with the lack of individuals carrying *SUFU* variants in our cohort, suggests that the true prevalence of BCNS in Norway may be somewhat higher than reported herein.

Despite new evidence of genotype–phenotype associations in BCNS, our study elucidates the great variation in disease burden that can be seen within the same *PTCH1* variant. This highlights the importance of early diagnosis and careful evaluation of all individuals with BCNS, and personalized follow-up, depending on symptoms.

All citizens in Norway have easy access to a free public health service with computer-based medical records. Thus, Norway is a country amenable to epidemiological studies being carried out. In the current study, complete physical examinations were performed on site by the authors, all radiographs were re-examined, detailed genetic findings were analysed and retrospective data were collected from computer-based medical records. Therefore, we can state that this is a comprehensively studied cohort of individuals with BCNS. Limitations include recollection bias in patient interviews, the potential of missing data in patient medical records and the possible under-reporting of individuals with BCNS in some geographical regions.

From this nationwide cohort of individuals with BCNS, we have expanded the number of pathogenic *PTCH1* variants, elucidated important clinical aspects in BCNS and revealed novel insights into genotype–phenotype associations, providing new implications for the management and follow-up of those with BCNS.

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Conflicts of interest

The authors declare the following conflicts of interest unrelated to the present work. K.H.B. has received an honorarium for acting as a meeting chair on behalf of LEO Pharma. J.P.H. is a consultant for PYX Therapeutics and AAVantgarde

Bio, and has given lectures for Santen and Novartis. S.S. has received speaker fees from Sanofi. K.H.H. has received honoraria for lectures from AbbVie and SUN Pharma. The other authors declare no conflicts of interest.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Ethics statement

The study protocol was approved by the Regional Committee for Medical and Health Research Ethics (approval number REK 753456) and the Oslo University Hospital Data Protection Officer. The study was performed in accordance with the Declaration of Helsinki.

Patient consent

Written patient consent for publication was obtained.

Supporting Information

Additional [Supporting Information](#) may be found in the online version of this article at the publisher's website.

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