ORIGINAL REPORT

Basal Cell Nevus Syndrome and Sporadic Basal Cell Carcinoma: A Comparative Study of Clinicopathological Features

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Basal cell nevus syndrome is caused by mutations in the Sonic hedgehog pathway and characterized by early-onset basal cell carcinoma. The features of basal cell carcinoma in basal cell nevus syndrome compared with sporadic basal cell carcinoma have not been explored. This study is a retrospective study of patients with basal cell nevus syndrome in two medical centres in Taiwan from 1991 to 2021 and patients with sporadic basal cell carcinoma excised from 2015 to 2020. An analysis of 18 patients with basal cell nevus syndrome showed an older mean age at the first diagnosis of basal cell carcinoma (37.5 years) than reported in Western countries. The majority of basal cell carcinomas were located in the head and neck region (80.7%), with nodular BCC being the most common tumour type (47.0%). Compared with sporadic basal cell carcinomas, basal cell carcinomas in basal cell nevus syndrome patients occurred more frequently on the scalp (34.7% vs 6.1%, $p < 0.001$). In addition, the superficial type of basal cell carcinoma was more likely to be seen in basal cell nevus syndrome (24.7% vs 10.4%, $p < 0.001$). The limitations were that some features of the basal cell nevus syndrome patients might not have been present yet at the time of examination or they did not receive thorough screening. In conclusion, the distinct features of basal cell carcinomas in basal cell nevus syndrome patients have important implications for the prevention, diagnosis, and management of basal cell carcinoma in basal cell nevus syndrome patients.

Key words: basal cell carcinoma; basal cell nevus syndrome; Gorlin syndrome; odontogenic keratocyst; pitting; PTCH1.

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SIGNIFICANCE

Our study highlighted an older average age at the first diagnosis of basal cell carcinoma in basal cell nevus syndrome at 37.5 years compared with basal cell nevus syndrome patients of Caucasian descent, suggesting that Asian ethnic backgrounds influence the timing and diagnosis of basal cell carcinoma. Furthermore, our research revealed that basal cell nevus syndrome-related basal cell carcinomas commonly manifested as superficial type and often occurred on the scalp, in contrast with sporadic cases. This distinction has not previously been mentioned and has important implications for prevention, diagnosis, and treatment.

Basal cell nevus syndrome (BCNS), also called Gorlin and Goltz syndrome or Gorlin syndrome, was first described in 1960 (1). The estimated prevalence is 1 in 57,000–256,000 (2). This syndrome is characterized by the presence of early-onset basal cell carcinoma (BCC), medulloblastoma, odontogenic keratocysts (OKCs), palmar or plantar pits, ovarian fibroma, lamellar calcification of the falx cerebri, macrocephaly, orofacial cleft, and skeletal malformations (3). BCNS has a spectrum of clinical manifestations (2, 4–9). This is due to loss-of-function germline mutations of the tumour suppressor genes in the Sonic hedgehog pathway, especially *PTCH1*, that lead to abnormal cell growth (10). The development of malignancies in BCNS was proposed to follow the two-hit suppressor gene model wherein the first hit was the germline *PTCH1* mutation and a second hit was needed, such as UV radiation (11). It is still unknown whether BCCs from BCNS and sporadic BCCs have different features given that both exhibit *PTCH1* mutation.

The aim of this study was to compare the BCC of BCNS patients and sporadic BCCs from 2 hospitals in Northern Taiwan. Specifically, both were compared in terms of age at tumour removal, location, and pathological subtypes. Moreover, the clinical profile of BCNS patients was also described. This study will provide additional knowledge and understanding of BCC and BCNS for early diagnosis and treatment.

MATERIALS AND METHODS

Study population

This study included all BCNS patients who were seen in National Taiwan University Hospital (NTUH) and Linkou Chang Gung Memorial Hospital (CGMH) from January 1991 to June 2021. Sporadic BCC is basal cell carcinoma in patients without BCNS, history of chronic arsenicism, or xeroderma pigmentosum. Those patients with sporadic BCC from January 2015 to September 2020 were included in the study. The Institutional Review Board of both hospitals approved this study (NTUH-REC No. 202106042RIND and CGMH-REC No. 202101417B0).

This retrospective study was done by reviewing the medical charts, pathology slides, imaging, and surgical records of relevant patients. The demographics, clinical characteristics, and genetic findings were reviewed.

The age at the first histology confirmed BCC, and number of tumours, location, and histopathological types were included. Those without well-described histological types and unavailable pathology slides were excluded in the analysis of tumour types. OKC was confirmed by histopathology and the total number of cysts was counted by imaging and surgical records.

Diagnostic criteria for BCNS

The diagnostic criteria used was by Bree and Shah (3) and Verkouteren et al. (12) (Table SI). A diagnosis of BCNS was made when either 2 major criteria were fulfilled, or 1 major and 2 minor criteria. The major criteria include BCC before 20 years of age or excessive number of BCCs, OKC of the jaw before 20 years of age, palmar or plantar pitting, lamellar calcification of falx cerebri, medulloblastoma and first-degree relative with BCNS. The minor criteria comprise multiple anomalies (Table SI).

Genetic testing

For the genetic screening in CGMH, DNA extracted from peripheral blood mononuclear cells was amplified with specific primers targeting all exons of *PTCH1* by PCR, followed by Sanger sequencing. If no mutation in *PTCH1* was detected, further testing of *PTCH2* and *SUFU* was proposed. While in NTUH, whole exome sequencing (WES) was performed to achieve 150X target depth. The sequencing reads were aligned to the human reference genome (UCSC, hg19 build) (13, 14). The genes in Sonic hedgehog signalling and XP family genes were examined specifically. Other detected mutations were reported if they were registered in the ACMG SF v3.0 list (15). The identified mutations were verified by Sanger sequencing. For those without detected *PTCH1* alteration, array comparative genomic hybridization (aCGH) was applied to detect copy number variants (CNVs).

Statistical analysis

Descriptive statistics was used for demographics and tumour characteristics. Data were rounded to the nearest tenth and presented as number (percentage) for discrete variables and mean with standard deviation (SD) for continuous variables. An independent two-tailed *t*-test was conducted for continuous variables after confirming normality of the data distribution by the Shapiro–Wilk test. Categorical data were analysed by using χ^2 test. Statistical analysis was performed using the GraphPad Prism software (https://www.graphpad.com/) version 8 and p-value <0.05 was considered as statistically significant.

RESULTS

Basic demographics and genetic data

Eighteen patients met the diagnostic criteria for BCNS and these patients had 259 histopathologically confirmed BCCs. For sporadic BCCs, 1,048 patients were included.

The clinical characteristics are listed in **Table I**. The majority of the study population had Fitzpatrick skin phototypes III–IV. The BCNS group had an equal male-to-female ratio, with a mean age of 46.8 years old. For the sporadic BCC group, the male-to-female ratio was also nearly equal (1:1.06). Sixteen (88.8%) out of 18 BCNS patients developed BCC and had a younger mean age at the first diagnosis of BCC than the sporadic BCC patients (37.5 years vs 69.6 years, $p<0.001$). The 2 BCNS patients without BCC were confirmed with *PTCH1* mutation and were aged 20 and 27 years old, respectively. The number of BCCs excised ranged from 1 to 74 and with an average of 17 BCCs. Fifteen patients had OKCs, with an average of 5 cysts per patient.

Six BCNS patients underwent genetic screening and all had heterozygous genetic alterations in *PTCH1* (Table I). The 3 patients who belonged to the same family received Sanger sequencing for *PTCH1* and had a mutation at splice acceptor (c.3450-1C > G), including a 20-year-old male who had no BCC at the time of examination (16). One patient had a different splice acceptor mutation (c.3169-1G>A) while another patient had a stop gain mutation (c.1606G>A). A 27-year-old male patient with multiple palmoplantar pits, 1 OKC, and falx cerebri calcification (**Fig. 1**A and B) had no BCC and subsequent analysis with aCGH confirmed a homozygous deletion in the 9q22.32-q22.33 region, encompassing the entire *PTCH1* gene (Fig. 1C). All 6 patients had OKCs, lamellar calcification of the falx cerebri, palmar or plantar pits, and ocular abnormalities. Five had macrocephaly while 4 had rib anomalies or other skeletal malformations.

Table I. Demographic and genetic findings and prevalence in the basal cell nevus syndrome (BCNS) group and sporadic basal cell carcinoma (BCC) group

Finding	BCNS $n=18$	Sporadic BCC $n=1,048$
Gender (male: female)	1:1	1:1.06
Mean current age (years)	46.8±17.1	73.2±13.4***
Patients with BCC	16#	1,048/1,048 (100)
Mean age at first BCC (years)	37.5±16.1	69.6±13.4***
Mean number of BCC removed	17.1±20.0	NA
Patients with jaw cysts	15	1***
Mean age at first jaw cyst (years)	29.8±18.0	NA
Mean number of jaw cysts*	5.4	NA
Mutations of *PTCH1*		
Splice acceptor, c.3450-1C>G	3†	NA
Stop gain, c.1606G>A	1	NA
Splice acceptor, c.3169-1G>A	1	NA
Microdeletion, 9q22.32-q22.33	1	NA

***, $p<0.001$.
#Two patients without BCC to date are 27 and 20 years old.
*Eleven of 15 patients with jaw cyst had a clear number of cysts shown by imaging or pathology. †Three cases are in the same family.
NA: not assessed.

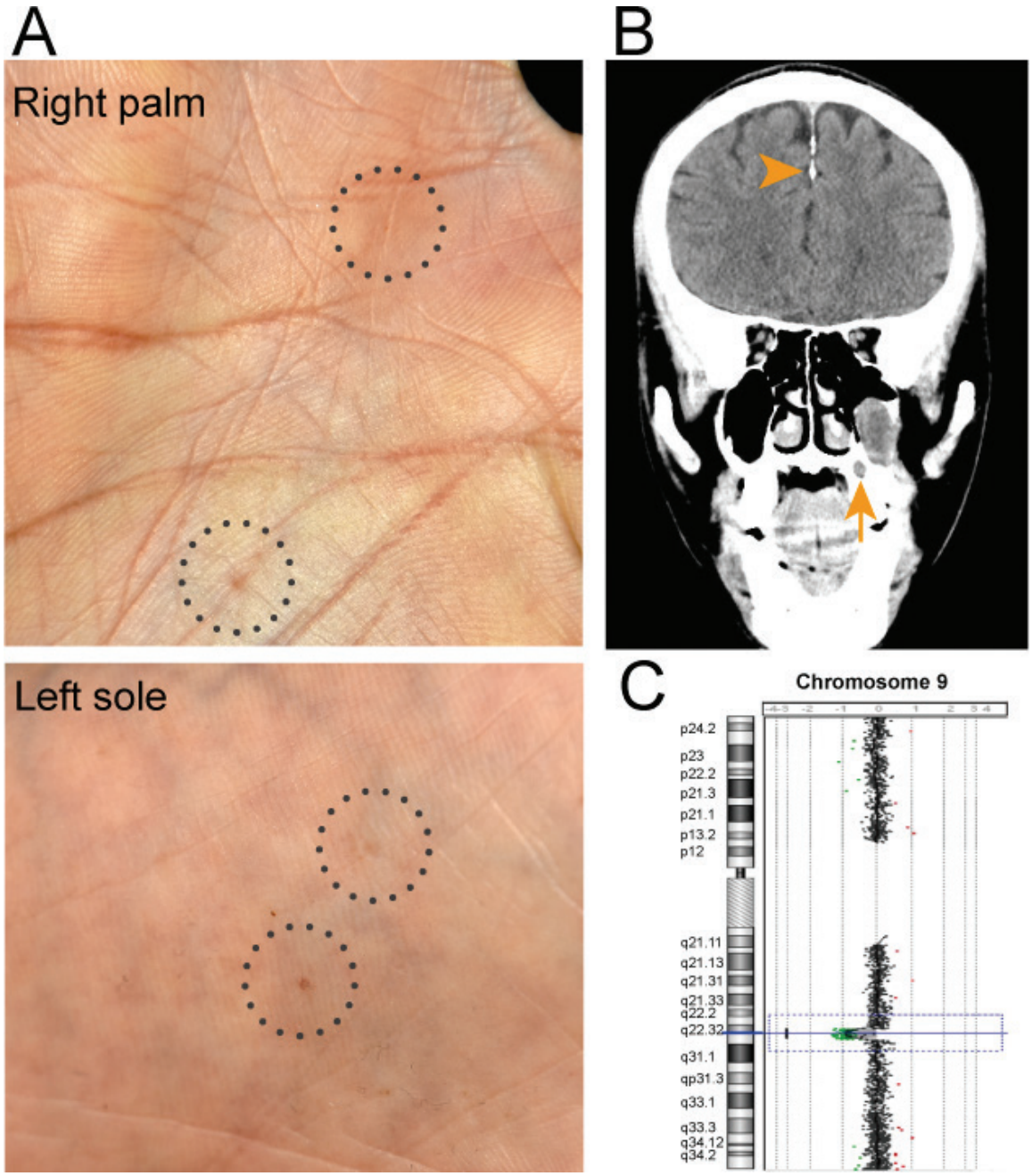

Fig. 1. Clinical and genetic findings in a 27-year-old male patient with basal cell nevus syndrome but without basal cell carcinoma. (A) Physical examination revealed multiple palmoplantar pits (dotted circles). (B) Head computed tomography scan demonstrating one odontogenic keratocyst in the left maxillary bone (arrow) and calcification of the falx cerebri (arrowhead). (C) The aCGH study identified a homozygous deletion, indicated by the rectangular box, spanning 9q22.32-q22.33 (chr9:97,320,223-100,506,985), encompassing the entire *PTCH1* gene region (chr9:98,205,262-98,279,253).

Clinical features of BCNS

The prevalence of the different clinical features in BCNS is summarized in Table SII. The most common finding was BCC, which was seen in 16 (88.9%) patients. Among those 16 patients, 2 had a BCC before 20 years old and 13 exhibited more than 2 BCCs. The second most common characteristic was OKC, noted in 15 (83.3%) patients. Six (33.3%) had OKCs prior to 20 years old. Lamellar calcification of the falx cerebri and palmar or plantar pits were seen in 13 (72.2%) patients each.

Location of BCC

A total of 259 BCCs were detected in the BCNS group and 1,048 cases of sporadic BCCs. In both groups, the most common site was the head and neck region, followed by the trunk, lower limbs, and upper limbs. BCNS patients developed significantly more BCCs on the scalp than those with sporadic BCCs ($p<0.001$) (**Table II**) In contrast, the patients with sporadic BCC had more BCCs located on the nose, nasolabial fold, and cheek.

Table II. Location of BCC in the BCNS group and sporadic BCC group

Location	BCNS *n* (%)	Sporadic BCC *n* (%)	*p*-value
Head and neck	209 (80.7)	865 (82.5)	0.488
Scalp	90 (34.7)	64 (6.1)	<0.001***
Scalp w/o RT	79/240 (32.9)	64 (6.1)	<0.001***
Forehead	9 (3.5)	42 (4.0)	0.692
Temple	2 (0.8)	15 (1.4)	0.402
Periorbital area[a]	32 (12.4)	81 (7.7)	0.018*
Ear	12 (4.6)	46 (4.4)	0.864
Nose	24 (9.3)	309 (29.5)	<0.001***
Nasolabial fold	2 (0.8)	44 (4.2)	0.007**
Perioral area[b]	5 (1.9)	37 (3.5)	0.191
Cheek	15 (5.8)	126 (12.0)	0.004**
Chin	1 (0.3)	16 (1.5)	0.147
Neck	5 (1.9)	20 (1.9)	0.981
Unknown	12 (4.6)	65 (6.2)	0.337
Trunk	29 (11.2)	111 (10.6)	0.778
Upper limb	8 (3.1)	20 (1.9)	0.240
Lower limb	10 (3.9)	39 (3.7)	0.916
Unknown	3 (1.2)	13 (1.2)	0.914
Total	259 (100)	1048 (100)	

[a]Includes supraorbital, infraorbital, upper eyelid, lower eyelid, eyebrow. and canthus. [b]Includes upper lip and lower lip.
BCNS: basal cell nevus syndrome; BCC: basal cell carcinoma; RT: radiotherapy; w/o: without. *$p<0.05$; **, $p<0.01$; ***, $p<0.001$.

Radiotherapy (RT) is a well-known risk factor for BCC and 2 of the patients with medulloblastoma received RT. One of them had all her 3 BCCs on the scalp and the other had 8 out of 16 BCCs on the scalp. After excluding the 2 patients with RT, the other 14 BCNS cases still had significantly more BCCs on the scalp than those with sporadic BCCs ($p<0.001$).

Pathological types of BCC

In this study, 247/259 and 866/1,048 BCCs had clearly defined pathologic types among the BCNS and sporadic BCC groups respectively (**Table III**). Most of the BCCs in the BCNS patients (89.5%) and the sporadic BCC patients (82.8%) had a solitary tumour type.

Table III. Pathological type of BCCs in the BCNS patients and the sporadic BCC patients

Tumour types	BCNS *n* (%)	Sporadic BCC *n* (%)	*p*-value
Solitary pattern:			
Superficial	61 (24.7)	90 (10.4)	<0.001***
Superficial w/o RT	57 (23.1)	90 (10.4)	<0.001***
Nodular[▲]	116 (47.0)	522 (60.2)	<0.001***
Micronodular	18 (7.3)	56 (6.5)	0.648
Infiltrative	7 (2.8)	36 (4.2)	0.341
Morphea	2 (0.8)	9 (1.0)	0.748
Metatypical	1 (0.4)	3 (0.3)	0.892
Miscellaneous[#]	16 (6.5)	2 (0.2)	<0.001***
Subtotal	221(89.5)	718 (82.8)	0.012*
Mixed pattern:			
Nodular-superficial	10 (4.0)	31 (3.7)	0.730
Nodular-micronodular	6 (2.4)	55 (6.3)	0.017*
Nodular-infiltrative	0 (0.0)	42 (4.8)	NA
Nodular-morphea	1 (0.4)	0 (0.0)	NA
Micronodular-infiltrative	2 (0.8)	6 (0.7)	0.848
Others (≤0.5%)	7 (2.8)	14 (1.6)	0.215
Subtotal	26 (10.5)	148 (17.2)	0.012*
Total	247(100)	866 (100)	

[▲]The nodular type includes the nodulocystic BCC. [#]The miscellaneous type includes BCC with follicular differentiation (trichoepithelioma-like), sebaceous differentiation, adenoid, fibroepithelioma of Pinkus, and keratotic BCC.
BCNS: basal cell nevus syndrome; BCC: basal cell carcinoma; RT: radiotherapy; w/o: without. *$p<0.05$; **, $p<0.01$; ***, $p<0.001$.

The most common tumour type in BCNS was nodular (47.0%), followed by superficial (24.7%), and micronodular (7.3%). Following a similar order of prevalence, in sporadic BCC patients, the most common tumour type was nodular (60.2%), followed by superficial (10.4%) and micronodular (6.5%). Statistically, the superficial type of BCC was significantly more common in BCNS than in sporadic cases ($p<0.01$). Also, the BCNS group showed a higher proportion of solitary pattern than the sporadic BCC group ($p=0.012$).

Twenty-six BCCs (10.5%) in the BCNS group and 148 BCCs (17.2%) in the sporadic BCC group had a mixed pattern. For the BCNS group, the most common mixed pattern was nodular-superficial (4.0%) followed by nodular-micronodular (2.4%). In the sporadic BCC group, the most common mixed pattern was nodular-micronodular (6.3%), followed by nodular-infiltrative (4.8%).

DISCUSSION

BCNS is a multisystem disease and its diagnostic criteria have been revised through the years (3, 5). BCC is a major criterion and can range from solitary to multiple lesions (2, 6, 9). The mean age at the first diagnosis of BCC in BCNS in this study was very close to the findings of Endo et al. in a Japanese population (8) (Table SIII). This age, however, is much older compared with other previous studies (6, 17). Regarding sporadic BCC cases, Asians typically developed their first BCC at an older age compared with Caucasians (68.9 years vs 58.3 years) (18). The development of BCCs at a later age in Asians, evident in both BCNS and sporadic BCC, suggests that factors such as geographical location, ethnic background, natural skin pigmentation, and differing sun protection practices may be contributory. These findings emphasize the need to consider these variables in the prevention, diagnosis, and treatment of BCC, particularly in diverse ethnic groups. Despite the older mean age of onset of BCC in BCNS in this study, 88.9% still developed BCC. This is similar to studies done in the USA and Switzerland in which >80% of patients with BCNS developed BCC (6, 17). This implies that even with the older age of onset of BCC, the majority of BCNS patients will still develop BCC, therefore continuous surveillance is important.

A study showed that calcification of the falx cerebri was seen in 79% of patients and this was also seen in 72.2% of patients in this study (19). There was also a high prevalence of OKCs across all studies. This highlights the importance of the digital Panorex examination of the jaw as OKC is one of the early clinical signs of BCNS (3). Medulloblastoma is the most common malignant tumour of childhood in BCNS (8, 20). In previous studies, the presence of medulloblastoma in BCNS was approxima-

tely 3–5% on average (6, 8, 21). This study showed a much higher percentage at 16.7%. There is a variability in disease manifestation as only 1 of the 3 patients in the same family developed medulloblastoma, despite the same underlying *PTCH1* mutation.

Basal cell carcinoma in BCNS and sporadic BCC

Research is lacking on the site of predilection of BCCs for BCNS. This study found that BCCs in both groups exhibited similar sites with the majority seen on sun-exposed areas, such as the head and neck. UV light is the primary cause of mutagenesis in BCCs that links to formation of cyclobutane dimers (22). A study revealed that 80% of BCCs of BCNS patients were seen on sun-exposed areas (17). Our BCNS patients had significantly more BCCs on the scalp than those with sporadic BCCs.

The histopathology of sporadic BCC cannot be distinguished from a BCC in a BCNS patient (2, 23). The nodular BCC is the most common tumour type of BCC followed by the superficial type in both BCNS patients and sporadic cases. A major finding in our study is that the superficial type of BCC was more likely to be seen in BCNS patients compared with those with sporadic BCCs (24.7% vs 10.4%, $p<0.001$).

The pathogenesis of the superficial type is still elusive and no particular mutation in addition to *PTCH1* is found to be relevant (24). The superficial type of BCC typically manifests as a flatter plaque that expands more across the surface of the skin, in contrast to the nodular type of BCC, which is more raised. Due to its less invasive growth pattern, the superficial BCC does not necessarily require deep excision. Those with superficial BCCs tended to be females, younger, and developed BCCs on the trunk or extremities. This subtype is also the most common tumour type associated with radiation therapy (25). Notably, the BCNS patients were found to be sensitive to both ionizing radiation and UV in terms of BCC formation (3, 26, 27). These findings suggest that superficial BCC might be more likely to result from a predisposition to rapidly accumulate DNA damage, such as BCNS, in response to ionizing radiation and UV exposure.

Mutation

Mutations in *PTCH1* were detected in 40–85% of BCNS patients, while mutations in *SUFU* were identified in only 5.3% (28, 29). No mutation in either *PTCH1* or SUFU was found in 20–27% of the BCNS patients (21, 29). In our study, only 6 patients received genetic screening but all of them were detected with mutations involving *PTCH1*. The *PTCH1* gene comprises 23 exons expanding 47 kb, making high-throughput sequencing an efficient tool to screen its mutations. A previous study showed *PTCH1* mutations of BCNS patients were mainly frameshift (50.7%), followed by nonsense and splicing site mutation (both 13.3%), large deletion (10.7%), and missense mutation (8%) (30). CNVs involving *PTCH1* were not very rare (31, 32). Among our patients, various kinds of mutations were noted but no missense variant was identified.

Limitations

This is a retrospective study and, thus, some features of the BCNS patients might not yet have been present at the time of examination or they did not undergo thorough screening. Another limitation in our study is the relatively small sample size. Additionally, a proportion of BCCs lacked a clearly defined pathologic tumour type. We have limited documentation concerning sun protection practices. Therefore, it is difficult to determine whether there are differences in sun protection practices between the 2 groups.

Conclusion

Our study presented 18 cases of BCNS from 2 hospitals in Northern Taiwan. Similar to previous studies, the most common manifestations were early-onset BCCs, OKCs, lamellar calcification of the falx cerebri, and palmar and plantar pits. The older age of onset of BCC in BCNS was noted in our population as well as in the Japanese population, potentially a shared feature among Asians, compared with Caucasians. When patients exhibit features of BCNS but do not meet the full criteria, genetic counselling and testing are valuable, especially considering the high detection rate of *PTCH1* mutations in our study. Our article identified 2 features frequently seen in BCNS patients compared with sporadic BCC: the superficial histological type and the common scalp location. These new findings may enhance comprehensive management for BCNS patients.

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The authors have no conflict of interest to declare.

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