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Cohort study of Gorlin syndrome with emphasis on standardised phenotyping and quality of life assessment

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Key words
nevoid basal cell carcinoma syndrome (NBCCS), basal cell nevus syndrome, Gorlin syndrome, Gorlin-Goltz syndrome, Basal cell carcinoma (BCC), quality of life in Gorlin syndrome, *PTCH1*, *SUFU*.

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Abstract

Background: Gorlin syndrome (nevoid basal cell carcinoma syndrome) is a rare genetic predisposition to basal cell carcinomas (BCC), keratocysts of the jaw and calcification of the falx cerebri among other clinical features. With the advent of sonic hedgehog inhibitors for the treatment of BCC, it is timely to establish a cohort of individuals with Gorlin syndrome and collect standardised phenotypic information on these individuals. Moreover, the health-related quality of life (QoL) in individuals with Gorlin syndrome is not well studied.
Aim: To establish a Victorian cohort of Gorlin syndrome and study the QoL in these individuals.
Methods: Phenotypic data were obtained by reviewing medical records of individuals attending two major tertiary/quaternary genetic referral centres in Victoria, followed by telephone or face-to-face interviews where possible. QoL information was obtained utilising the AQoL-6D quality of life survey form.
Results: The median number of BCC in the 19 individuals studied was 17.5 (interquartile range 3–70). The number of patients with ≥100 BCC in this group was similar to a previously described national cohort (22.2 vs 27% respectively). A total of 58% of referrals to the genetics clinics originated from maxillofacial surgeons and 42% from dermatologists. Individuals with ≥100 BCC had worse median QoL scores compared to those with <100 BCC (36 vs 29, *P*-value of 0.031).
Conclusion: The clinical features in our cohort were congruent with those previously described in Australia. The QoL is adversely correlated with increased BCC burden.

Introduction

Gorlin syndrome, also known as the nevoid basal cell carcinoma syndrome (NBCCS), is an autosomal dominant developmental syndrome, which causes various congenital abnormalities and a predisposition to basal cell carcinomas (BCC).[1,2] The condition is highly penetrant; however, the clinical features can be variable.[3] The Australian prevalence, ascertained on clinical criteria, was estimated to be 1:164 000 in 1994.[4]

There are two currently used clinical criteria for the diagnosis of Gorlin syndrome (Table 1).[2,5]

A mutation in the gene *PTCH1* accounts for 50–90% of cases,[6,7] with the other implicated genes being *SUFU*[8] and *PTCH2*.[9] Approximately 15–27% of clinical cases do not have a detectable mutation.[10] The gene product of *PTCH1* acts as a tumour suppressor in the hedgehog signalling pathway, and the abrogation of this pathway explains the increased propensity for BCC.[11–15]

Our study aimed to annotate phenotypically a Victorian cohort of individuals with Gorlin syndrome. It is well recognised that proximity to the equator increases the risk for skin cancers.[16–19] Therefore, with possibly less ultraviolet light exposure in Victoria compared with the northern states, we aimed to assess the BCC burden in Victorian patients. Visible skin lesions, particularly on the face, have been associated with depression and reduced quality of life (QoL).[20–22] We report health-related QoL in this cohort correlated with the clinical features, with particular reference to the number of BCC.

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Table 1 Clinical diagnostic criteria

1993 criteria by Evans *et al*. (Diagnosis fulfilled with two major or one major and two minor criteria)	1997 modified criteria by Kimonis (Diagnosis fulfilled with two major or one major and two minor criteria)
Major criteria	Major criteria
1. >2 BCC or 1 under 30 years or >10 basal cell naevi	1. >2 BCC or 1 under the age of 20 years
2. Odontogenic keratocyst (proven on histology), or polyostotic bone cyst	2. Odontogenic keratocysts of jaw (proven on histology)
3. ≥3 palmar or plantar pits	3. ≥3 more palmar or plantar pits
4. Ectopic calcification: lamellar or early (<20 years) falx calcification	4. Bi-lamellar calcification of the falx cerebri
5. Family history of Gorlin syndrome	5. Bifid, fused or markedly splayed ribs
	6. First-degree relative with NBCC syndrome
Minor criteria	Minor criteria
1. Congenital skeletal anomaly: bifid, fused, splayed or missing rib, or bifid, wedged, or fused vertebra	1. Macrocephaly determined after adjustment for height
2. Head circumference >97th percentile, with frontal bossing	2. Congenital malformations: cleft lip or palate, frontal bossing, 'coarse face', moderate or severe hypertelorism
3. Cardiac or ovarian fibroma	3. Other skeletal deformities: Sprengel deformity, marked pectus deformity, marked syndactyly of the digits
4. Medulloblastoma	4. Radiological abnormalities: bridging of the sella turcica, vertebral anomalies such as hemiverterbrae, fusion or elongation of the vertebral bodies, modelling defects of the hands and feet, or flame-shaped lucencies of the hands or feet
5. Lymphomesenteric cysts	5. Ovarian fibroma
6. Congenital malformation: cleft lip and/or palate, polydactyly, eye anomaly (cataract, coloboma, micropthalmia	6. Medulloblastoma

BCC, basal cell carcinomas; NBCC, nevoid basal cell carcinoma.

Methods

Study sites and ethical oversight

Human Research Ethics Committees at Melbourne Health (MH) and the Royal Children's Hospital (RCH) have reviewed and approved the study (MH project number: 2013.314, RCH project number: HREC 34283A).

Inclusion and exclusion criteria

Database searches were conducted in Melbourne Health Department of Genetics, including the Familial Cancer Centre (FCC) and The Victorian Clinical Genetics Services (VCGS). All individuals who attended these two genetic centres and were clinically diagnosed with Gorlin syndrome based on the above criteria, or were otherwise clinically suspected to have Gorlin syndrome by a geneticist, were included. Potential adult participants who were unable to consent to the study, deceased participants with no next of kin and children without a parent to consent were excluded. Individual file reviews were conducted, and participants were also surveyed over the phone to obtain more details of their medical history. Patients who attended the FCC and were thus recruited were clinically assessed at their appointment after written informed consent was obtained.

Data collection

Information on skin type was collected based on skin colour and tanning ability and translated to the Fitzpatrick skin-type scale (Appendix I).[23] We chose to ascertain QoL using the AQoL-6D questionnaire as Australian population norms for this questionnaire were available.[24] The QoL questionnaire ascertains the patient's self-reported current health-related QoL. It was undertaken retrospectively and does not reflect the participants' QoL at the time of diagnosis, genetic testing or BCC surgery.

Genetic testing

The majority of *PTCH1* testing was performed through Sanger sequencing, although the more recent tests were performed through next generation sequencing and Sanger verification of variants. Copy number variant analysis on all samples was undertaken either through multiplex ligation-dependent probe amplification or comparative genomic hybridisation (CGH) array-based techniques by the testing laboratory.

All *SUFU* tests were performed through massively parallel sequencing with variants confirmed by Sanger sequencing in addition to CGH array-based copy number variation analysis by the testing laboratory.

Statistical analysis

Descriptive analysis was undertaken, and results were reported as median with interquartile range (IQR) for

continuous data and *n* (%) for categorical data. The Wilcoxon rank-sum test was used to determine any associations between total number of BCC or QoL and the various categorical variables, such as mutation status, sun exposure, jaw cysts and occupation. Spearman's correlation was used to determine an association between total number of BCC and patients' QoL. Fisher exact test was used to determine any associations between *PTCH1* mutation and patients' clinical characteristics. Level of significance was set at $P < 0.05$ for all tests. The data analysis was performed using Stata12 (StataCorp, College station, TX, USA).

Results

Cohort demographics

A total of 19 patients (12 from MH and 7 from VCGS) was recruited to the study. Demographic characteristics of the study cohort are presented in Table 2. There were two families each with three affected members, whilst the other participants were unrelated. The median age at diagnosis of Gorlin syndrome was 18 (IQR 14–55).

Table 2 Demographics

Total	*n* = 19
Gender	
Male (%)	8 (42.1)
Female (%)	11 (57.9)
Age at recruitment, mean (SD) (years)	38.6 (17.8)
<18	1 (5.3)
≥18	18 (94.7)
Ethnicity	
Caucasian (%)	12 (63.2)
Other (%)	7 (36.8)
Occupation	
Indoor (%)	16 (84.2)
Outdoor (%)	2 (10.5)
Missing (%)	1 (5.3)
Relationship status	
Married/de-facto (%)	13 (68.4)
Single (%)	5 (26.3)
Child (%)	1 (5.3)
Smoking	
Current (%)	1 (5.3)
Past (%)	6 (31.5)
Never (%)	11 (57.9)
Missing (%)	1 (5.3)
Fitzpatrick skin type	
Type I (%)	1 (5.3)
Type II (%)	12 (63.2)
Type III (%)	5 (26.2)
Type IV–VI (%)	0 (0)
Missing (%)	1 (5.3)
Childhood sun exposure†	
High (%)	11 (57.9)
Low (%)	5 (26.3)
Missing (%)	3 (15.8)

†Self-reported.

Table 3 Predominant Evans or Kimonis criteria features in the cohort

Clinical features	Numbers† (%)
Basal cell carcinomas	14/18 (77.8)
Macrocephaly	10/15 (66.7)
Odontogenic keratocyst (Jaw cyst)	12/19 (63.2)
Palmar/plantar pits	10/18 (55.6)
Calcification of falx	9/14 (64.3)
Family history of Gorlin syndrome	8/17 (47.1)
Scoliosis	7/17 (41.2)

†The denominator varies in each category as full clinical information was not available for all 19 participants.

The majority of genetic referrals originated from maxillofacial surgeons (57.9%, 11/19) and the remainder (42.1%, 8/19) from dermatologists. Eight individuals were diagnosed with Gorlin syndrome either at or before the age of 18, with seven of them diagnosed by a maxillofacial surgeon. There were three patients who did not fulfil either diagnostic criteria but underwent genetic testing because of the presence of multiple BCC or jaw cysts.

Clinical features

Basal cell carcinomas (Table 3)

A total of 7 out of the 8 male participants (87.5%) and 7 out of 10 females (70%) had a history of BCC (BCC data were unavailable for one female). The median number of BCC in this cohort was 17.5, with a median of 5 on the face and 12.5 on the body. Of the six participants aged ≤25, three had not developed BCC yet, one participant had three, and one had 30 BCC. No data on

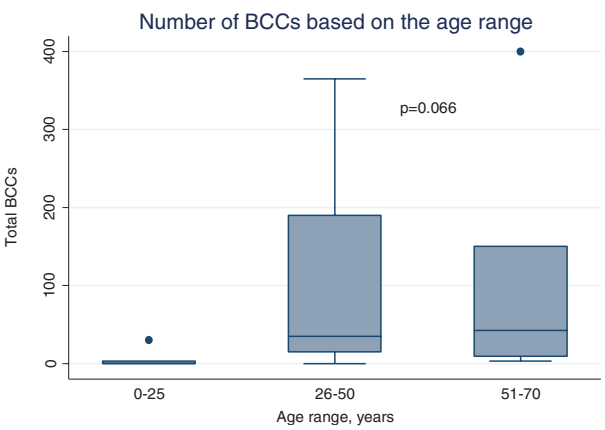

Figure 1 Cumulative number of basal cell carcinomas (BCC) against age.

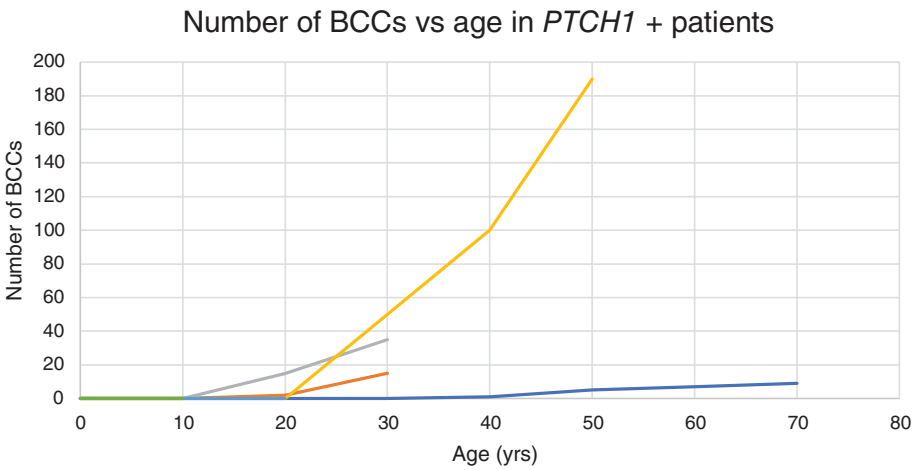

Figure 2 Cumulative number of basal cell carcinomas (BCC) with age in individual *PTCH1* mutation-positive patients. Note: Patients 5 and 6 have not developed any BCC to their respective ages of 23 and 15. (——), Patient 1; (——), patient 2; (——), patient 3; (——), patient 4; (——), patient 5; (——), patient 6.

BCC were available for one young participant. The cumulative number of BCC with age is depicted in Figure 1. The median number of BCC in our cohort was 0 under the age of 25, 35 between the ages 26 and 50 and 42.5 between ages 51 and 70. The youngest age of onset of BCC was 12 years in a man who has subsequently developed 30 BCC by his current age of 25. The four individuals with documented absence of BCC are all currently aged younger than 30. The number of BCC in *PTCH1* and *SUFU* mutation-positive individuals with increasing age is depicted in Figures 2 and 3.

Distribution of BCC based on Fitzpatrick skin type is depicted in Figure 4.

There were four individuals who had >100 BCC. Their characteristics are listed in Table 4. All four fulfilled both Evans and Kimonis diagnostic criteria for Gorlin syndrome.

Jaw cysts

Odontogenic keratocysts as the second most common feature, being present in 12 of the 19 (63.2%) participants. A total of 11 patients was referred to the genetic clinic by maxillofacial surgeons, and 1 patient (developed his first BCC at the age of 12) was referred by his dermatologist.

All individuals with jaw cysts fulfilled the clinical diagnostic criteria except one, who was tested on the basis of isolated jaw cysts. A total of 7 out of 12 underwent genetic testing for *PTCH1*, with 5 of these participants having a pathogenic mutation.

A total of 7 of the 12 participants with jaw cysts also had BCC. The most jaw cysts described was 20 in a 22-year-old woman whose diagnosis of Gorlin syndrome was made at the age of 8 because of multiple jaw cysts and medulloblastoma. She has not developed BCC and has not undergone genetic testing to date.

Palmar and plantar pits

All 10 patients with >3 palmar/plantar pits fulfilled the clinical diagnostic criteria. Nine of these participants also had jaw cysts, and seven had BCC. Five underwent genetic testing of *PTCH1*, and a pathogenic mutation was identified in all cases.

Calcification of the falx

Calcification of falx was observed in 64.3% (9/14) of the participants. Of these, seven were female, and two were male. All participants with falx calcification fulfilled the

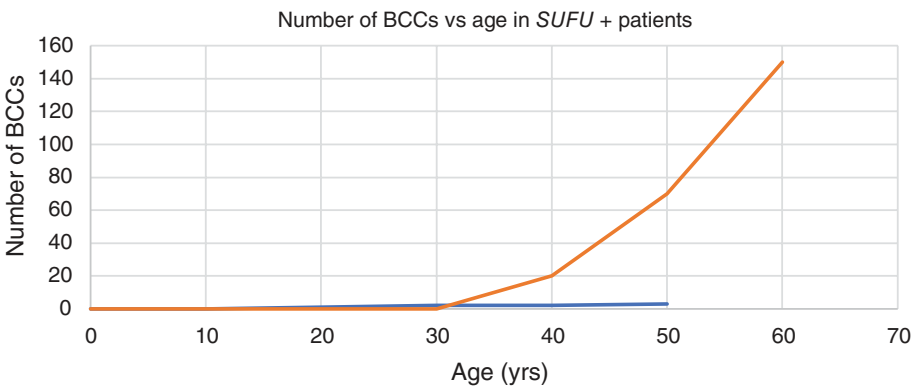

Figure 3 Cumulative number of basal cell carcinomas (BCC) with age in individual *SUFU* mutation-positive patients. (——), Patient 1; (——), patient 2.

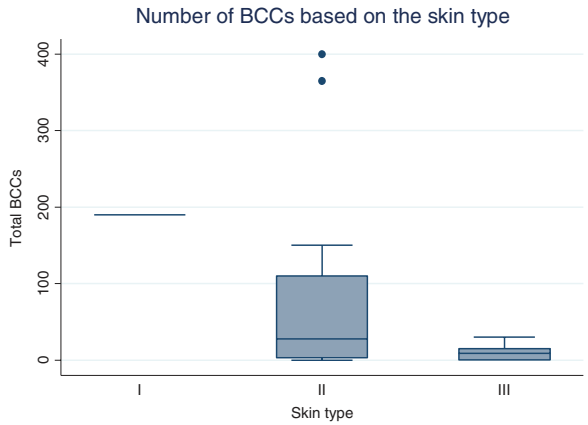

Figure 4 Median number of basal cell carcinomas (BCC) based on Fitzpatrick skin type.

clinical diagnostic criteria. Five of these nine participants with falx calcification underwent genetic testing, with two found to harbour a *PTCH1* mutation and two found to have *SUFU* mutations.

Other features

A family history of Gorlin syndrome, diagnosed clinically in at least one first-degree relative, was present in 8/17 (47.1%) participants. Macrocephaly, present in 10/15 (66.7%) participants, was the most common of the minor Evans/Kimonis diagnostic features. Of the 19 participants, 4 (21.1%) had a high arched palate. Scoliosis was present in 7 of 17 (41.2%) individuals; 9 of 15 (60%) participants reported childhood fractures, and 3 participants had mild intellectual disability. Medulloblastoma was present in one patient.

Genetic testing results

Of 19 participants, 11 (68.4%) underwent genetic testing for *PTCH1*. Of the 11 patients tested, 6 (54.5%) were found to have a pathogenic *PTCH1* mutation and 5 did not. Two participants were not offered testing but were categorised as *PTCH1* -ve as their similarly clinically affected sibling had no *PTCH1* mutation on testing.

Two unrelated patients who did not harbour a *PTCH1* mutation were found to have a mutation in *SUFU*. The characteristics of the *PTCH1* mutation-positive patients compared to those with negative results are listed in Table 5. There were four different *PTCH1* mutations and two different *SUFU* mutations identified in the cohort.

The presence of palmar/plantar pits was the only clinical feature that reached statistical significance between the *PTCH1* +ve and *PTCH1* −ve groups (*P*-value of 0.005).

QoL characteristics

The AQoL-6D questionnaire is designed to assess health-related QoL in adults only. Four participants were excluded from this analysis as a result of being <18, having a mild intellectual disability, being deceased or having circumstances that would independently impact QoL.

The overall and age-based QoL scores were calculated on a weighted scale to enable comparison with population norms. In the weighted scales, scores closer to 1.0 reflect good health-related QoL outcomes, and scores closer to 0 reflect worse outcomes. Raw scores were used to calculate the QoL scores for all other features and compared within the cohort as no population norms were available for these features. When using the raw scores, higher scores reflect worse QoL

Table 4 Characteristics of individuals with >100 BCC

>100 BCC	Patient 1	Patient 2	Patient 3	Patient 4
Number on face	10	50	200	220
Number on body	180	100	200	145
Gender	Male	Female	Male	Female
Current age	46	62	55	38
Ethnic origin	Caucasian	Caucasian	Caucasian	Caucasian
Skin type	I	II	II	II
Childhood sun exposure	High	High	High	High
History of smoking	N	Y	Y	N
Age smoking ceased	N/A	18	25	N/A
Squamous cell carcinomas	2	0	1	0
Number of jaw cysts	0	0	4	3
Palmar/Plantar pits	N	N	N	Y
PTCH1 mutation +ve	Y	N	NT	NT
SUFU mutation +ve	N	Y	NT	NT

BCC, basal cell carcinoma; NT, not tested (genetic testing not undertaken).

Table 5 Description of mutations in this cohort along with salient phenotypic features

Mutation	Clinical features							
	Proband/ FDR	Current age (years)	No. BCC	No. keratocysts	Palmar or plantar pits	Falx calcification	Macrocephaly	Other
PTCH1:c.3152G>A (p. W1051X) in exon 18	Proband	Died at 70	9	5	Yes	No	Yes	Lung cancer (smoker), neurofibroma of stomach
PTCH1:c.3152G>A (p. W1051X) in exon 18	FDR of above	23	0	4	Yes	Yes	No	Craniosynostosis
PTCH1:c.3152G>A (p. W1051X) in exon 18	FDR of above	26	15	3	Yes	Yes	No	Telecanthus
PTCH1:c.2460C>A (p. Y820X) NM_000264.3 in exon 15	Proband	46	190	0	No	N/A	No	2 SCC (high occupational sun exposure), unilateral post axial polydactyly, speech impairment
PTCH1:c.202-2A>G, NM_000264.3	Proband	27	35	14	Yes	Yes	Yes	Bifid ribs, Sprengel deformity, midface hypoplasia
0.7 Mb del in chromosome 9q22.32 involving *PTCH1* and 5 other genes	Proband	15	0	5	Yes	Yes	Yes	Mild gross motor developmental delay
SUFU: c. 756+1G>A in intron 6	Proband	57	3	0	No	No	Yes	Benign facial folliculosebaceous hamartomas, two children died of medulloblastoma under the age of two[25]
SUFU:c.1365+2T>A in intron 11†	Proband	62	150	0	No	Yes	Yes	Childhood medulloblastoma in a grandson

†This canonical splice site mutation 2 base pairs after the end of exon 11 of *SUFU* is uniformly predicted to completely abolish the donor splice site of intron 11, leading to synthesis of abnormal protein. As this is a novel mutation with no previous documentation of its functional impact, RNA studies are currently under way to fully understand the functional consequences of this mutation. BCC, basal cell carcinoma; FDR, first-degree relative; SCC, squamous cell carcinomas.

outcomes. The AQoL-6D survey questionnaire can be divided into six different dimensions based on the questions in the survey. Table 6 compares age-related QoL scores and the various dimensions with the population norms. In summary, there were no statistically significant differences between our cohort and the population norms.

Multiple variables were compared between the different participants within the cohort as mentioned in Table 7. The only variable that reached statistical significance within this cohort was the presence of ≥100 BCC when compared with individuals with <100 BCC ($P = 0.031$). Individuals with scoliosis had lower QoL scores compared with those who did not have scoliosis ($P = 0.08$). QoL characteristics are described in Table 8.

Discussion

In this study, we have collected standardised phenotyping information on a Victorian cohort with Gorlin syndrome and analysed the health-related QoL associated with the diagnosis.

Phenotypic information

BCC in the cohort

The background rate of BCC is very high in the Australian general population, with a reported incidence of 884 per 100 000 person-years as recorded in 2002.[26] The incidence of BCC in Gorlin syndrome varies significantly between individuals and can range from several hundred to relatively few, but they tend to occur at an earlier age and at a higher frequency than in the average population.[27] Within Australia, the rates of non-melanoma skin cancer (NMSC) vary with latitude.[28] The prevalence of NMSC in Queensland recorded between 1986 and 1987 was 5%.[17] However, as BCC are not reportable to the cancer registry in Australia, the numbers of BCC nationwide were difficult to obtain. The prevalence of BCC in our cohort (77.8%) is concordant with the numbers reported by Shanley *et al*. in a large Australian cohort,[4] although we acknowledge that with our small numbers, no definite conclusions can be made. Interestingly, in our cohort, the median number of BCC in patients with a *PTCH1* mutation did not vary from those without a *PTCH1* mutation.

Table 6 Characteristics of *PTCH1* mutation +ve and mutation –ve patients

	PTCH1 +ve (n = 6)†	*PTCH1* –ve (n = 7)‡	*P*-value
Patients with BCC (%)	4/6 (66.7)	5/7 (71.4)	1.000
Median number of BCC (IQR)	12 (0–35)	40 (3–70)	0.572
Patients with jaw cysts (%)	5/6 (83.3)	2/7 (28.6)	0.103
Patients with palmar/plantar pits (%)	5/6 (83.3)	0/7 (0)	0.005
Patients with calcification of the falx (%)	2/2 (100)	3/6 (50.0)	0.464
Family history of Gorlin (%)	3/5 (60)	3/6 (50.0)	1.000
Macrocephaly	2/3 (66.7)	3/6 (50.0)	1.000

The varying denominator represents the subgroup of patients in whom testing was undertaken and in whom the phenotypic information was available. The majority of *PTCH1* testing was performed through Sanger sequencing, although the more recent tests were performed through next generation sequencing and Sanger verification of variants. Copy number variant analysis on all samples was undertaken either through multiplex ligation-dependent probe amplification or comparative genomic hybridisation (CGH) array-based techniques by the testing laboratory. All *SUFU* tests were performed through massively parallel sequencing with variants confirmed by Sanger sequencing in addition to QMPS or CGH array-based copy number variation analysis by the testing laboratory. †Four of these six individuals were probands, and two were relatives who underwent confirmatory genetic testing. ‡Two of these patients were identified to have a *SUFU* mutation. BCC, basal cell carcinoma.

All participants in this study had Fitzpatrick skin type I–III, with the most common being type II. Therefore, this study is more representative of individuals with white skin type and the BCC numbers cannot be translated to other skin types or ethnic backgrounds. It is important to note that we only had one patient with Fitzpatrick type I skin. Therefore, the high number of BCC seen in this individual is not necessarily representative of all Gorlin syndrome patients with type I skin.

Childhood sun exposure has a stronger association with later BCC development compared to adult sun exposure.[29] We looked at the impact of high versus low childhood sun exposure on the number of BCC. The confounding factor in our cohort was that the mean age of the low childhood sun exposure group was significantly lower, 24 years, than the high childhood sun exposure group, 43.5 years. It is not possible to predict if this younger population will develop more BCC with time. Therefore, it is difficult to draw conclusions on the effect of childhood sun exposure from this cohort.

We have shown the trend towards the increase of total number of BCC with ageing in patients with Gorlin syndrome (P = 0.066) in Figure 1. This could statistically be proven in a larger cohort.

Table 7 QoL scores compared with population norms

QoL scores in Gorlin syndrome cohort		QoL scores in general population (population norms)		*P*-value
	Weighted QoL scores		Weighted QoL scores	
Overall	0.84	Overall	0.80	0.3
Age range (years)		Age ranges in years		
≤25	0.92	15–24	0.78	
		25–34	0.82	
26–50	0.84	35–44	0.83	
		45–54	0.79	
51–70	0.79	55–64	0.80	
		65–74	0.77	
		75+	0.75	
Dimensions		Dimensions		
Independent living	0.94	Independent living	0.91	0.452
Relationships	0.92	Relationships	0.89	0.473
Mental health	0.64	Mental health	0.63	0.835
Coping	0.85	Coping	0.81	0.310
Pain	0.82	Pain	0.79	0.565
Senses	0.89	Senses	0.91	0.500

QoL, quality of life.

Other features

As odontogenic keratocysts are a unique finding, this prompts specialist referral earlier with a potentially earlier diagnosis in comparison to BCC, which are more common in the population and therefore likely to be managed without a specialist referral. In keeping with the lack of genotype phenotype correlation described with *PTCH1* mutations in the literature,[30] in our cohort, a father with a *PTCH1* mutation had 9 BCC at the age of 70, whilst one of his daughters had 15 BCC at the age of 26, and the other had not developed any BCC at the age of 23. This supports evidence that modifying genes or environmental factors modify the age of onset of BCC in Gorlin syndrome.[31] Surprisingly, other than the presence of palmar/plantar pits, no other clinical features were significantly different between the *PTCH1*+ and *PTCH1* –ve groups. It is possible that the small numbers in this study has increased the standard error of the mean and masked any differences.

Health-related QoL

We found that the QoL in our ≤25-year-old participants (n = 6) was better than the population norms. One of the factors influencing this may be a selection bias, with the cohort formed of patients willing to participate in the study, indicating their interest in their health outcomes. As the phenotypes were similar between the *PTCH1*+

and *PTCH1*– patients, the lack of difference in the QoL scores between these two groups was not surprising.

The adverse effect of scoliosis on QoL is worthy of further analysis in a larger cohort as it has been noted in literature that scoliosis negatively affects health-related QoL significantly.[32]

Evaluating the clinical utility of genetic testing

The utility of genetic testing in those who fulfil the diagnostic criteria for Gorlin syndrome is largely to allow predictive testing of family members. Early genotypic diagnosis allows better reinforcement of sun avoidance and recruitment to strict surveillance programmes. Conversely, a negative predictive test provides marked reassurance. Some families, depending on the severity and impact of Gorlin syndrome, may choose to explore options such as pre-natal diagnosis or pre-implantation genetic diagnosis.

In patients who do not fulfil the clinical criteria but have some suggestive features, genetic testing may confirm a diagnosis, providing certainty with regards to the diagnosis as well as opening up targeted therapeutic options. In this category, those who do not have a mutation suggestive of Gorlin syndrome present a diagnostic and management challenge. As there are some age-related manifestations of Gorlin syndrome, the surveillance in these patients should be individualised based on their clinical features at the time of review.

A *SUFU* mutation should be suspected in Gorlin syndrome families with a history of medulloblastoma and macrocephaly.[33] The utility in offering *SUFU* genetic testing is high in such families as surveillance through annual brain MRI may be relevant in children with a mutation in this gene.[10]

Surveillance and follow-up

The number of participants in this study was smaller than expected because of loss of contact with many paediatric cases when they transitioned to adult care. This raises the issue of awareness and education of primary care physicians whose clinics these patients are likely to continue to attend and seek advice from. The majority of BCC are likely to be diagnosed and treated by General Practitioners. We suggest that primary care physicians should be educated about the genetic nature of this condition and the clinical diagnostic criteria. It is particularly important as this may facilitate the identification of other family members who may be at risk, so they can make informed choices in terms of occupational or recreational sun exposure as well as genetic testing.

Table 8 QoL characteristics

Feature	Median (IQR) AQoL-6D score†
Gender	
Male	29 (27–36)
Female	30 (29–35)
Relationship status	
Married or in a relationship	29.5 (27–35)
Single or not in a relationship	30 (29–43)
Past history of smoking	
Yes	33 (30–36)
No	27 (25–43)
Number of BCC	
<100	29 (27–30)
≥100	36 (30–43)
Scoliosis	
Yes	27 (25–30)
No	33 (29.5-39.5)
Underwent genetic testing (n = 13)	30 (27–35)
Not yet undergone genetic testing (n = 6)	29 (26–41)
PTCH1 testing	
PTCH1+	28.5 (24.5–36.5)
PTCH1–	30.5 (30–38.5)

†The scores used here are overall scores and not individually weighted to the various dimensions. BCC, basal cell carcinoma; IQR, interquartile range; QoL, quality of life.

Limitations

The number of participants in this study was small. In addition, the retrospective nature of this study meant that not all data fields could be collected in all individuals.

Conclusions

The number of people with >100 BCC in this Victorian subpopulation of Gorlin syndrome patients was not significantly different to the national average for this condition despite the difference in the solar ultraviolet radiation exposure because of the latitude differences. The clinical features in our cohort were congruous with those previously described in Australia.

The QoL is adversely affected by the number of BCC; however, this needs to be verified in a larger study as the numbers were small. General practitioners need to be educated about the features of Gorlin syndrome to aid in earlier diagnosis and treatment. The relationship between QoL and scoliosis needs to be examined further.

Future directions

Collection of a cohort of patients with Gorlin syndrome with standardised phenotypic information is highly relevant in the current era of therapeutic trials

for BCC in Gorlin syndrome, such as oral and topical sonic hedgehog inhibitors.[34–37] This well-annotated clinical cohort can be drawn upon for future trials. Patients with jaw cysts could potentially benefit from any future trials of sonic hedgehog inhibitors for keratocysts in Gorlin syndrome such as described by Goldberg *et al.*[37]

The current study has been set up as a platform for a future study of a Victorian cohort that could act as a registry for therapeutic studies. The data recorded in the registry would form a baseline so that metrics could be devised to measure response to treatment accordingly.

References

1 Lo Muzio L. Nevoid basal cell carcinoma syndrome (Gorlin syndrome). *Orphanet J Rare Dis* 2008; **3**: 32.

2 Evans DG, Ladusans EJ, Rimmer S, Burnell LD, Thakker N, Farndon PA. Complications of the naevoid basal cell carcinoma syndrome: results of a population based study. *J Med Genet* 1993; **30**: 460–4.

3 Kiwilsza M, Sporniak-Tutak K. Gorlin-Goltz syndrome – a medical condition requiring a multidisciplinary approach. *Med Sci Monit* 2012; **18**: RA145–53.

4 Shanley S, Ratcliffe J, Hockey A, Haan E, Oley C, Ravine D *et al.* Nevoid basal cell carcinoma syndrome: review of 118 affected individuals. *Am J Med Genet* 1994; **50**: 282–90.

5 Kimonis VE, Goldstein AM, Pastakia B, Yang ML, Kase R, DiGiovanna JJ *et al.* Clinical manifestations in 105 persons with nevoid basal cell carcinoma syndrome. *Am J Med Genet* 1997; **69**: 299–308.

6 Evans DG, Farndon PA. Nevoid basal cell carcinoma syndrome. In: Pagon RA, Adam MP, Ardinger HH, Wallace SE, Amemiya A, Bean LJH, Bird TD, Ledbetter N, Mefford HC, Smith RJH, Stephens K, eds. *GeneReviews*. Seattle, WA: University of Washington; 1993.

7 Lindstrom E, Shimokawa T, Toftgard R, Zaphiropoulos PG. PTCH mutations: distribution and analyses. *Hum Mutat* 2006; **27**: 215–9.

8 Pastorino L, Ghiorzo P, Nasti S, Battistuzzi L, Cusano R, Marzocchi C *et al.* Identification of a SUFU germline mutation in a family with Gorlin syndrome. *Am J Med Genet A* 2009; **149A**: 1539–43.

9 Fan Z, Li J, Du J, Zhang H, Shen Y, Wang CY *et al.* A missense mutation in PTCH2 underlies dominantly inherited NBCCS in a Chinese family. *J Med Genet* 2008; **45**: 303–8.

10 Smith MJ, Beetz C, Williams SG, Bhaskar SS, O'Sullivan J, Anderson B *et al.* Germline mutations in SUFU cause Gorlin syndrome-associated childhood medulloblastoma and redefine the risk associated with PTCH1 mutations. *J Clin Oncol* 2014; **32**: 4155–61.

11 Farndon PA, Del Mastro RG, Evans DG, Kilpatrick MW. Location of gene for Gorlin syndrome. *Lancet* 1992; **339**: 581–2.

12 Hahn H, Wicking C, Zaphiropoulous PG, Gailani MR, Shanley S, Chidambaram A *et al.* Mutations of the human homolog of Drosophila patched in the nevoid basal cell carcinoma syndrome. *Cell* 1996; **85**: 841–51.

13 Johnson RL, Rothman AL, Xie J, Goodrich LV, Bare JW, Bonifas JM *et al.* Human homolog of patched, a candidate gene for the basal cell nevus syndrome. *Science* 1996; **272**: 1668–71.

14 Gailani MR, Bale SJ, Leffell DJ, DiGiovanna JJ, Peck GL, Poliak S *et al.* Developmental defects in Gorlin syndrome related to a putative tumor suppressor gene on chromosome 9. *Cell* 1992; **69**: 111–7.

15 Levanat S, Gorlin RJ, Fallet S, Johnson DR, Fantasia JE, Bale AE. A two-hit model for developmental defects in Gorlin syndrome. *Nat Genet* 1996; **12**: 85–7.

16 Bauer A, Diepgen TL, Schmitt J. Is occupational solar ultraviolet irradiation a relevant risk factor for basal cell carcinoma? A systematic review and meta-analysis of the epidemiological literature. *Br J Dermatol* 2011; **165**: 612–25.

17 Green A, Beardmore G, Hart V, Leslie D, Marks R, Staines D. Skin cancer in a Queensland population. *J Am Acad Dermatol* 1988; **19**: 1045–52.

18 English DR, Kricker A, Heenan PJ, Randell PL, Winter MG, Armstrong BK. Incidence of non-melanocytic skin cancer in Geraldton, Western Australia. *Int J Cancer* 1997; **73**: 629–33.

19 Marks R, Jolley D, Dorevitch AP, Selwood TS. The incidence of non-melanocytic skin cancers in an Australian population: results of a five-year prospective study. *Med J Aust* 1989; **150**: 475–8.

20 Ghajarzadeh M, Ghiasi M, Kheirkhah S. Associations between skin diseases and quality of life: a comparison of psoriasis, vitiligo, and alopecia areata. *Acta Med Iran* 2012; **50**: 511–5.

21 Tidman MJ. Prompt treatment of acne improves quality of life. *Practitioner* 2012; **256**: 15–7.

22 Mathias SD, Chren MM, Colwell HH, Yim YM, Reyes C, Chen DM *et al.* Assessing health-related quality of life for advanced basal cell carcinoma and basal cell carcinoma nevus syndrome: development of the first disease-specific patient-reported outcome questionnaires. *JAMA Dermatol* 2014; **150**: 169–76.

23 Fitzpatrick TB. The validity and practicality of sun-reactive skin types I through VI. *Arch Dermatol* 1988; **124**: 869–71.

24 Richardson JR, Peacock SJ, Hawthorne G, Iezzi A, Elsworth G, Day NA. Construction of the descriptive system for the assessment of quality of life AQoL-6D utility instrument. *Health Qual Life Outcomes* 2012; **10**: 38.

25 Mann K, Magee J, Guillaud-Bataille M, Blondel C, Bressac-de Paillerets B, Yeatman J *et al.* Multiple skin hamartomata: a possible novel clinical presentation of SUFU neoplasia syndrome. *Fam Cancer* 2015; **14**: 151–5.

26 Staples MP, Elwood M, Burton RC, Williams JL, Marks R, Giles GG. Non-melanoma skin cancer in Australia: the 2002 national survey and trends since 1985. *Med J Aust* 2006; **184**: 6–10.

27 Berlin NI, Van Scott EJ, Clendenning WE, Archard HO, Block JB, Witkop CJ *et al.* Basal cell nevus syndrome. Combined clinical staff conference at the National Institutes of Health. *Ann Intern Med* 1966; **64**: 403–21.

28 Perera E, Gnaneswaran N, Staines C, Win AK, Sinclair R. Incidence and prevalence of non-melanoma skin cancer in Australia: a systematic review. *Australas J Dermatol* 2015; **56**: 258–67.

29 Gallagher RP, Hill GB, Bajdik CD, Fincham S, Coldman AJ, McLean DI

et al. Sunlight exposure, pigmentary factors, and risk of nonmelanocytic skin cancer. I. Basal cell carcinoma. *Arch Dermatol* 1995; **131**: 157–63.
30 Wicking C, Shanley S, Smyth I, Gillies S, Negus K, Graham S *et al.* Most germline mutations in the nevoid basal cell carcinoma syndrome lead to a premature termination of the PATCHED protein, and no genotype-phenotype correlations are evident. *Am J Hum Genet* 1997; **60**: 21–6.
31 Yasar B, Byers HJ, Smith MJ, Lear J, Oudit D, Bholah Z *et al.* Common variants modify the age of onset for basal cell carcinomas in Gorlin syndrome. *Eur J Hum Genet* 2015; **23**: 708–10.
32 Freidel K, Petermann F, Reichel D, Steiner A, Warschburger P, Weiss HR. Quality of life in women with idiopathic scoliosis. *Spine (Phila Pa 1976)* 2002; **27**: E87–91.
33 Brugieres L, Remenieras A, Pierron G, Varlet P, Forget S, Byrde V *et al.* High frequency of germline SUFU mutations in children with desmoplastic/nodular medulloblastoma younger than 3 years of age. *J Clin Oncol* 2012; **30**: 2087–93.
34 Sekulic A, Migden MR, Oro AE, Dirix L, Lewis KD, Hainsworth JD *et al.* Efficacy and safety of vismodegib in advanced basal-cell carcinoma. *N Engl J Med* 2012; **366**: 2171–9.
35 Tang JY, Mackay-Wiggan JM, Aszterbaum M, Yauch RL, Lindgren J, Chang K *et al.* Inhibiting the hedgehog pathway in patients with the basal-cell nevus syndrome. *N Engl J Med* 2012; **366**: 2180–8.
36 Saran A. Basal cell carcinoma and the carcinogenic role of aberrant Hedgehog signaling. *Future Oncol* 2010; **6**: 1003–14.
37 Goldberg LH, Landau JM, Moody MN, Kazakevich N, Holzer AM, Myers A. Resolution of odontogenic keratocysts of the jaw in basal cell nevus syndrome with GDC-0449. *Arch Dermatol* 2011; **147**: 839–41.

Appendix I

Fitzpatrick skin types[23]

Skin type	Skin colour	Sunburn	Tan
I	White	Yes	No
II	White	Yes	Minimal
III	White	Yes	Yes
IV	White	No	Yes
V	Brown	No	Yes
VI	Black	No	Yes