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

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Abstract:

Background:

Gorlin syndrome (Nevoid Basal Cell Carcinoma Syndrome) is a rare genetic predisposition to basal cell carcinomas (BCCs), keratocysts of the jaw and calcification of the falx cerebri amongst other clinical features. With the advent of sonic hedgehog inhibitors for the treatment of BCCs, 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. We aimed to establish a Victorian cohort of Gorlin syndrome and study the QoL in these individuals.

Methods:

Phenotypic data was 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 an AQoL-6D quality of life survey form.

Results:

The median number of BCCs in the 19 individuals studied was 17.5 (IQR 3-70). The number of patients with ≥ 100 BCCs in this group was similar to a previously described national cohort (22.2% vs 27%, respectively). Fifty-eight percent of referrals to the genetics clinics originated from maxillofacial surgeons and 42% from dermatologists. Individuals with ≥ 100 BCCs had worse median QoL scores compared to those with < 100 BCCs (36 vs 29, p value 0.031)

Conclusions:

The clinical features in our cohort were congruent with those previously described in Australia. The QoL is adversely correlated with increased BCC burden.

Key Words: Nevoid Basal Cell Carcinoma Syndrome, NBCCS, Basal Cell Nevus Syndrome, Gorlin Syndrome, Gorlin-Goltz syndrome, Basal Cell Carcinomas, BCC, Quality of life in Gorlin syndrome, PTCH1, SUFU

Figure 1.jpg

Figure 2.jpg

Figure 3.jpg

Figure 4.jpg

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Background and 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 (BCCs) ^{1,2}. The condition is highly penetrant, however, the clinical features can be variable ³. The Australian prevalence, ascertained on clinical criteria, was estimated in 1994 as 1:164,000 ⁴.

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

Table 1

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 abrogation of this pathway explains the increased propensity for BCCs ¹¹⁻¹⁵.

Our study aimed to phenotypically annotate a Victorian cohort of individuals with Gorlin syndrome. It is well recognized that proximity to equator increases the risk for skin cancers ¹⁶⁻¹⁹. Therefore, with possibly less UV exposure in Victoria in comparison to 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 BCCs.

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 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 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 (see appendix 1)²³. We chose to ascertain QoL using the AQoL-6D questionnaire as Australian population norms for this questionnaire were available²⁴. 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 MLPA or CGH-array based techniques by the testing laboratory.

All *SUFU* tests were done 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.

Statistical analysis:

Descriptive analysis was undertaken and results reported as median with interquartile range (IQR) for continuous data and n(%) for categorical data. Wilcoxon rank-sum test was used to determine any associations between total number of BCCs or QoL, and the various categorical variables such as mutation status, sun exposure, jaw cysts, occupation. Spearman's correlation was used to determine an association between total number of BCCs and patients' QoL. Fisher's exact test was used to determine any associations between *PTCH1* mutation and patient's 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:

Nineteen patients (12 from MH and 7 from VCGS) were recruited to the study. Demographic characteristics of the study cohort are presented in table 2. There were 2 families each with 3 affected members, whilst the other participants were unrelated. The median age at diagnosis of Gorlin syndrome was 18 (IQR 14-55).

Table 2

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 7 of them diagnosed by maxillofacial surgeon. There were 3 patients who did not fulfil either diagnostic criteria, however, underwent genetic testing due to the presence of multiple BCCs or jaw cysts.

Clinical features:

Table 3

Basal cell carcinomas:

Seven out of the 8 male participants (87.5%) and 7 out of 10 females (70%) had a history of BCCs. (BCC data was unavailable in one female). The median number of BCCs in this cohort was 17.5, with a median of 5 on the face and 12.5 on the body. Of the 6 participants aged ≤ 25 , three had not developed BCCs yet, one had 3 and one had 30 BCCs. No data on BCCs were available for one young participant. The cumulative number of BCCs with age is depicted in figure 1. The median number of BCCs in our cohort was 0 under the age of 25, 35 between the ages 26 and 50, 42.5 between ages 51 and 70. The youngest age of onset of BCCs was 12 years in a man who has subsequently developed 30 BCCs by his current age of 25. The 4 individuals with documented absence of BCCs are all

currently aged less than 30. The number of BCCs in *PTCH1* and *SUFU* mutation positive individuals with increasing age is depicted in figures 3 and 4.

Figure 1

Distribution of BCCs based on Fitzpatrick skin type is depicted in figure 2.

Figure 2

Figure 3

Figure 4

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

Table 4

Jaw cysts:

Odontogenic keratocysts were the second most common feature, being present in 12 of the 19 (63.2%) participants. Eleven patients were referred to the genetic clinic by maxillofacial surgeons and one 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. Seven out of 12 underwent genetic testing for *PTCH1* with 5 of these participants having a pathogenic mutation.

Seven of the 12 participants with jaw cysts also had BCCs. The most jaw cysts described was 20 in a 22 year old female whose diagnosis of Gorlin syndrome was made at the age of 8 due to multiple jaw cysts and medulloblastoma. She has not developed BCCs 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 7 had BCCs. Five underwent genetic testing of *PTCH1* and a pathogenic mutation was identified in all cases.

Calcification of the falx:

Calcification of falx was seen in 64.3% (9/14) of the participants. Of these, 7 were female and 2 were male. All participants with falx calcification fulfilled the clinical diagnostic criteria. Five of these nine participants with falx calcification underwent genetic testing, with 2 found to harbour a *PTCH1* mutation and 2 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 commonest of the minor Evans/ Kimonis diagnostic features. Four of the 19 participants (21.1%) had a high arched palate. Scoliosis was present in 7/17 (41.2%) individuals. 9/15 (60%) participants reported childhood fractures. 3 participants had mild intellectual disability. Medulloblastoma was present in one patient.

Genetic testing results:

Eleven out of nineteen (68.4%) participants underwent genetic testing for *PTCH1*. Six of the 11 patients tested (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 4 different *PTCH1* mutations and 2 different *SUFU* mutations identified in the cohort.

Table 5

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).

Table 6

Quality of life characteristics:

The AQoL-6D questionnaire is designed to assess health related QoL in adults only. Four participants were excluded from this analysis, due to either being <18, having a mild intellectual disability, being deceased or having circumstances which would independently impact on 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 outcomes. The AQoL-6D survey questionnaire can be divided into 6 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.

Table 7

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 presence of ≥ 100 BCCs, when compared with individuals with < 100 BCCs (p value= 0.031). Individuals with scoliosis had lower QoL scores compared with those who did not have scoliosis (p value =0.08).

Table 8

Discussion:

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

Phenotypic information:

BCCs in the cohort:

The background rate of BCCs is very high in the Australian general population with a reported incidence of 884 per 100,000 person-years as recorded in 2002²⁶. The incidence of basal cell carcinomas (BCCs) 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 higher frequency than in the average population²⁷. Within Australia, the rates of non-melanoma skin cancer (NMSC) varies with latitude²⁸. The prevalence of NMSC in Queensland recorded between 1986 and 1987 was 5%¹⁷. However, as BCCs are not reportable to cancer registry in Australia, the numbers of BCCs nationwide were difficult to obtain. The prevalence of BCCs in our cohort (77.8%) is concordant with the numbers reported by Shanley et al in a large Australian cohort⁴, although we acknowledge that with our small numbers, no definite conclusions can be made. Interestingly, in our cohort, the median number of BCCs in patients with a *PTCH1* mutation did not vary from those without a *PTCH1* mutation.

All people in this study had Fitzpatrick skin type I-III with most common being type II. Therefore, this study is more representative of the Caucasian population 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 BCCs 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 exposure²⁹. We looked at the impact of high versus low childhood sun exposure on the number of BCCs. The confounding factor in our cohort was that the mean age of the low childhood sun exposure group was significantly lower, being 24, than the high childhood sun exposure group, being 43.5. It is not possible to predict if this younger population will develop more BCCs with time.

Therefore, it is difficult to draw conclusions on the effect of childhood sun exposure from this cohort.

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

Other features:

As odontogenic keratocysts are a unique finding, this prompts specialist referral earlier with a potentially earlier diagnosis in comparison to BCCs 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 literature³⁰, in our cohort, a father with a *PTCH1* mutation had 9 BCCs at the age of 70, whilst one of his daughters had 15 BCCs at the age of 26 and the other had not developed any BCCs at the age of 23. This supports the evidence³¹. 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 on QoL with scoliosis is worthy of further analysis in a larger cohort as it has been noted in literature that scoliosis negatively affects health related QoL significantly³².

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 programs. 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 fulfill 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 individualized 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 macrocephaly³³. 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 gene¹⁰.

Surveillance and follow-up:

The number of participants in this study was smaller than expected due to 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 BCCs 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 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.

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:

In conclusion, the number of people with >100 BCCs 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 due to the latitude differences. The clinical features in our cohort were congruous with those previously described in Australia.

The quality of life is adversely affected by the number of BCCs, 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 standardized phenotypic information is highly relevant in the current era of therapeutic trials for BCCs in Gorlin syndrome such as oral and topical sonic hedgehog inhibitors³⁴⁻³⁷. 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 al³⁷.

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

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Figure Legends

Figure 1: Cumulative number of BCCs against age

Figure 2: Median number of BCCs based on Fitzpatrick skin type

Figure 3: Cumulative number of BCCs with age in individual *PTCH1* mutation positive patients.

Note: Patients 5 and 6 have not developed any BCCs to their respective ages of 23 and 15.

Figure 4: Cumulative number of BCCs with age in individual *SUFU* mutation positive patients

Tables

Table 1: Clinical diagnostic criteria

1993 criteria by Evans et al (Diagnosis fulfilled with 2 major or 1 major and 2 minor criteria)	1997 modified criteria by Kimonis (Diagnosis fulfilled with 2 major or 1 major and 2 minor criteria)
Major criteria	Major criteria
<ol style="list-style-type: none"> 1. >2 BCCs or 1 under 30 years, or > 10 basal cell naevi 2. Odontogenic keratocyst (proven on histology), or polyostotic bone cyst 3. ≥3 palmar or plantar pits 4. Ectopic calcification: lamellar or early (<20 years) falx calcification 5. Family history of Gorlin syndrome 	<ol style="list-style-type: none"> 1. >2 BCCs or 1 under the age of 20 years 2. Odontogenic keratocysts of jaw (proven on histology) 3. ≥3 more palmar or plantar pits 4. Bi-lamellar calcification of the falx cerebri 5. Bifid, fused or markedly splayed ribs 6. First degree relative with NBCC syndrome
Minor criteria	Minor criteria
<ol style="list-style-type: none"> 1. Congenital skeletal anomaly: bifid, fused, splayed or missing rib, or bifid, wedged, or fused vertebra 2. Head circumference >97th centile, with frontal bossing 3. Cardiac or ovarian fibroma 4. Medulloblastoma 5. Lymphomesenteric cysts 6. Congenital malformation: cleft lip and/or palate, polydactyly, eye anomaly (cataract, coloboma, microphthalmia) 	<ol style="list-style-type: none"> 1. Macrocephaly determined after adjustment for height 2. Congenital malformations: cleft lip or palate, frontal bossing, "coarse face", moderate or severe hypertelorism 3. Other skeletal deformities: Sprengel deformity, marked pectus deformity, marked syndactyly of the digits 4. Radiological abnormalities: bridging of the sella turcica, vertebral anomalies such as hemivertebrae, fusion or elongation of the vertebral bodies, modelling defects of the hands and feet, or flame shaped lucencies of the hands or feet 5. Ovarian fibroma 6. Medulloblastoma

Table 2: Demographics

Total		n=19
Gender		
	Male (%)	8 (42.1)
	Female (%)	11 (57.9)
Age at recruitment, mean (SD)		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)

*Note: the denominator varies in each category as full clinical information was not available on all 19 participants

Table 4: Characteristics of individuals with >100 BCCs

>100 BCCs	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	Y	N	NT	NT
+ve SUFU mutation	N	Y	NT	NT
+ve				

NT: Not tested (genetic testing not undertaken)

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

Mutation	Proband/FDR*	Current Age	No. of BCCs	No. of keratocysts	Clinical Features		Macrocephaly	Other
					Palmar or plantar pits	Falx calcification		
<i>PTCH1</i> :c.3152G>A (p.W1051X) in exon 18	Proband	Died at 70	9	5	Yes	No	Yes	Lung cancer (smoker), neurofibroma of stomach
<i>PTCH1</i> :c.3152G>A (p.W1051X) in exon 18	FDR of above	23	0	4	Yes	Yes	No	Craniosynostosis
<i>PTCH1</i> :c.3152G>A (p.W1051X) in exon 18	FDR of above	26	15	3	Yes	Yes	No	Telecanthus
<i>PTCH1</i> :c.2460C>A (p.Y820X) NM_000264.3 in exon 15	Proband	46	190	0	No	N/A	No	2 SCCs [#] (high occupational sun exposure), unilateral post axial polydactyly, speech impairment
<i>PTCH1</i> : 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 <i>PTCH1</i> and 5 other genes	Proband	15	0	5	Yes	Yes	Yes	Mild gross motor developmental delay
<i>SUFU</i> : 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 ¹
<i>SUFU</i> :c.1365+2T>A in intron 11 [^]	Proband	62	150	0	No	Yes	Yes	Childhood medulloblastoma in a grandson

*FDR= First Degree Relative

[#]SCCs=Squamous Cell Carcinomas

[^] 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

Table 6: Characteristics of *PTCH1* mutation +ve and mutation -ve patients

	<i>PTCH1</i> +ve (n=6) [#]	<i>PTCH1</i> -ve (n=7) [*]	<i>p-value</i>
Patients with BCCs (%)	4/6 (66.7)	5/7 (71.4)	1.000
Median number of BCCs (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

[#]Four of these 6 individuals were probands and 2 were relatives who underwent confirmatory genetic testing

^{*}Two of these patients were identified to have a *SUFU* mutation.

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 MLPA or CGH-array based techniques by the testing laboratory. All *SUFU* tests were done 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.

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 ranges in 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

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 BCCs[#]	
<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)
<i>PTCH1</i> testing	
<i>PTCH1</i> +	28.5 (24.5-36.5)
<i>PTCH1</i> -	30.5 (30-38.5)

*The scores used here are overall scores and not individually weighted to the various dimensions

APPENDIX 1

Fitzpatrick skin types

Fitzpatrick Skin Types			
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

Fitzpatrick, T.B., *The validity and practicality of sun-reactive skin types I through VI*. Arch Dermatol, 1988. **124**(6): p. 869-71.

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