Review Article

Genetic factors underlying basal cell carcinoma risk: a narrative review

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Background and Objective: Basal cell carcinoma (BCC) is the most common type of malignant tumor and a subtype of non-melanoma skin cancer (NMSC). It has a slow progression, metastasizes extremely rarely, but sometimes causes severe local tissue destruction. The constantly increasing incidence of BCC results from a complex interaction between environmental, genetic, and other risk factors. Several oncogenes and antioncogenes have been proved to be involved in BCC pathogenesis, including the vital effector portions of the hedgehog (HH) signaling pathway (i.e., *PTCH1*, *PTCH2*, *SMO* or *SUFU* genes), MC1R, and TP53. HH signaling pathway dysregulation is related to dysplasia and carcinoma, including Gorlin syndrome (GS) and sporadic cancers. Mutations caused by ultraviolet (UV) light and/or copy-loss heterozygosity of related genes lead to the abnormal signaling pathway activation, responsible for over 90% of the BCC cases. This review intends to provide a revision of the genetic factors affecting BCC.

Methods: The PubMed database was searched with a search algorithm [(basal cell carcinoma) OR (BCC)] AND [(gene) OR (pathway)], till May 2021, to filter out relevant publications. Relevant researches omitted from this search algorithm were also selected from the specific full-text papers reference lists. No language restrictions included in our search.

Key Content and Findings: This review provides a revision of several potential mechanisms that may involve in BCC carcinogenesis. Some genetic agents have been considered the risk factors for BCC, including the vital effector portions of the HH signaling pathway, MC1R, and TP53. Certain inherited disorders, including Gorlin syndrome, xeroderma pigmentosum, and Bazex-Dupré-Christol syndrome, are considered genetic risk factors for BCC, predisposing BCC at an early age. Other genes, such as *BRCA1*, *BRCA2*, *CTLA-4*, *AS3MT*, *N-Myc* and Hippo-YAP pathway target genes (*MYCN PTPN14*, *PPP6C*, *STK19*, *LATS1*) also show the potential relevance in BCC tumorigenesis and progression.

Conclusions: The hereditary basis of BCCs can vary from targeted mutations in the HH signaling pathway to deficiencies of tumor suppressors and melanin synthesis. These may lead to DNA damage and promotes BCC growth. The knowledge and characterization of the BCC genetic factors could underlie the development of new therapies.

Keywords: Basal cell carcinoma (BCC); hedgehog signaling pathway; *PTCH 1; TP53; MC1R*

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Introduction

Basal cell carcinoma (BCC) is the most prevalent form of malignant skin cancer with a good prognosis, originating from the basal layer of the epidermis and its appendages (1-4). Some clinical features, e.g., rodent ulcers, telangiectasias, pigmented and erosion areas, can be considered a characteristic of this disease (5,6). The incidence rates of BCC worldwide increase continuously owing to an aging population and widespread sun exposure. Still, the incidence estimation is imprecise since few population-based cancer registries and active nationwide surveillance systems exist in most countries and regions for monitoring and reporting the incidence of BCC (7,8). While BCC's biological mechanism(s) is still unclear, environmental and genetic factors are primarily related to its pathogenesis (9,10). Some genetic agents have been considered the risk factors for BCC, e.g., Patched 1 (*PTCH1*) genes. In most cases, keratinocyte transformation occurs when the function of multiple genes (proto-oncogenes, tumor suppressor genes, and essential housekeeping genes) affected by mutations, causing hyperactivation of the HH protein family, leading to cell cycle deregulation, implicated as drivers in BCC formation (11,12). Moreover, the *TP53* tumor suppressor gene is also commonly involved in the pathogenesis of BCC (3).

Therefore, this review provides an overview of BCC's genetic pathogenesis. In this review, the PubMed database was searched with a search algorithm [(basal cell carcinoma) OR (BCC)] AND [(gene) OR (pathway)] to filter out relevant publications. Relevant researches omitted from this search algorithm were also selected from the specific full-text papers reference lists. We present the following article in accordance with the Narrative Review reporting checklist (available at https://fomm.amegroups.com/article/view/10.21037/fomm-21-70/rc).

Methods

The PubMed database was searched with a search algorithm [(basal cell carcinoma) OR (BCC)] AND [(gene) OR (pathway)], till May 2021, to filter out relevant publications. Relevant researches omitted from this search algorithm were also selected from the specific full-text papers reference lists. No language restrictions included in our search (*Table 1*).

Hedgehog (HH) signaling pathway

The HH signaling pathway, i.e., the Hedgehog-Patched-Smoothened (Hh-Ptch-Smo), is an evolutionarily conserved pathway of signal transmission from the cell membrane to the nucleus, plays a vital role in the normal embryonic development of vertebrates (13) (*Figure 1*). Generally, the HH pathway is only active during embryonic development. A secreted protein, sonic HH ligand, binds to the transmembrane regulator receptor protein PTCH1 and inactivates it (14). Thus, the pathway is primarily inactive or poorly active in the adult organism. However, it can be activated in somatic and pluripotent stem cells in specific circumstances, such as tissue repair (15-17).

Malfunction or unusual activation of the pathway is associated with dysplasia and carcinogenesis (18-20). It behaves differently in different stages of various tumors, such as Gorlin syndrome (GS) (also known as Nevoid Basal Cell Carcinoma Syndrome, NBCCS), sporadic BCC, and medulloblastomas (21), among others. Gene variations (ligand-independent signaling) or HH signaling molecules overexpression (ligand-dependent signaling—autocrine or paracrine) can lead to aberrant activation of the pathway (22).

There are three proteins—HH ligand, PTCH, and Smoothened (SMO)—that participate in the activation of HH signaling (23).

The HH signaling pathway could be activated by SMO-activating variants or inactivating variants of *PTCH1* or *SUFU* (HH signaling negative regulator), leading to constitutive activation of HH signaling without ligand (24). This connection was first found in GS patients with a *PTCH1* mutation on chromosome 9 (14). According to the HH model, *SMO* repression is relieved following mutational inactivation of *PTCH1* (25). Sonic HH (SHH), which is the strongest pathway activator, bind to *PTCH1* and remove it from primary cilium and result in stimulation of *SMO*, triggers the activation of the transcription factors Gli1 (glioma-associated oncogene homolog) and/or Gli2 (26-30), resulting in cell proliferation. It has been involved in the development of BCC and other tumors, especially meningiomas and rhabdomyosarcomas (21).

Germline or somatic inactivating (loss-of-function) mutations of *PTCH1*, *PTCH2*, or *SUFU*, the activating (gain of function) mutations of *SMO*, or the amplification of *GLI2* lead to the aberrant activation of HH (31), are responsible for over ninety percent of BCC cases in both sporadic BCC and GS. Mutations in the *SUFU* gene are the least common type have been seen in sporadic BCC (24) and specific hereditary syndromes, e.g., a subset of Gorlin BCC cases (5%) (32), multiple congenital infundibulocystic BCC syndrome cases (33), as well as some childhood-

Table 1 The search strategy summary

Items	Specification
Date of search	04 May 2021
Databases and other sources searched	PubMed
Search terms used	[(basal cell carcinoma) OR (BCC)] AND [(gene) OR (pathway)]
Timeframe	Till 04 May 2021
Inclusion and exclusion criteria	No searching restrictions
Selection process	All search and selection were done by Sitong Ju independently

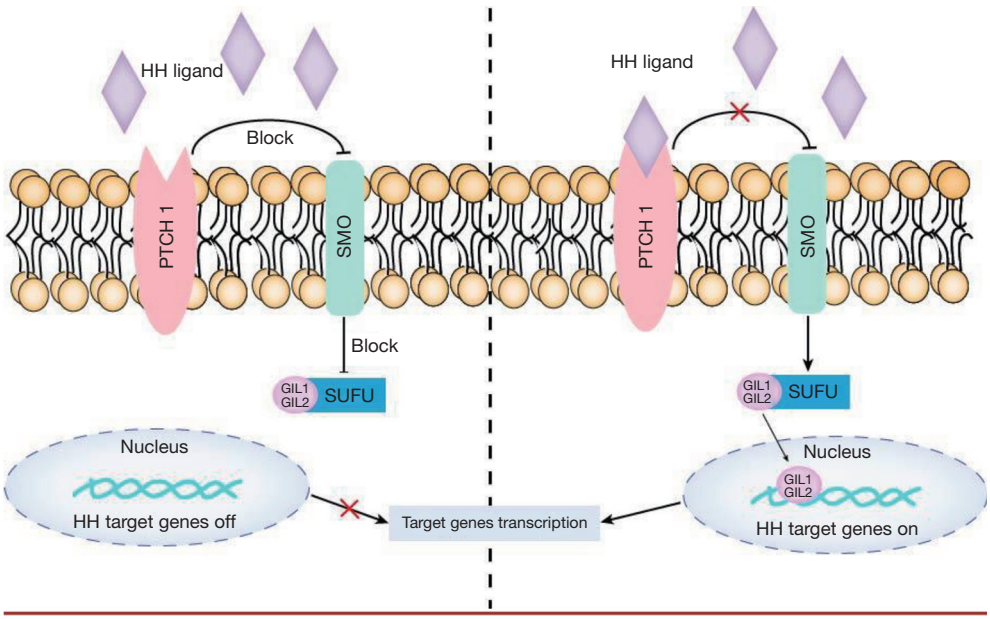

Figure 1 Hedgehog (HH) signaling pathway.

medulloblastoma families with "Gorlin-like" phenotype and hamartomatous skin lesions (34). Thus, there are three types of medulloblastoma caused by the aberrant activation of the HH signaling pathway: (I) NBCCS with *SUFU* mutations (20-fold increased risk than in the classic form) (32,35); (II) (a classic form of) NBCCS with *PTCH1* mutations, and (III) NBCCS with *PTCH2* mutations (a milder form than the previous one) (36). Incidentally, the *PTCH2* gene mutation may also be the cause of sporadic BCC or sporadic medulloblastoma (37).

PTCH

PTCH is the receptor for HH protein, and two PTCH homologs have been isolated in vertebrates: *PTCH1* and *PTCH2* (38), both encode transmembrane receptors of the patched gene family in the SHH pathway and have diverse functions depending on their differential expression in epidermal development (26,39).

PTCH1 gene, primarily expressed in mesenchymal cells, is located on chromosome 9q22.3. It contains twenty-three exons and encodes a glycoprotein of 1,447 amino acids. PTCH1 binds to SHH proteins resulting in the stimulation of SMO, which acts as a transmembrane receptor of the HH signaling pathway and directs the embryonic growth of various organs in vertebrates (13,14,40). Its dysregulation is known to be essential in tumorigenesis, including BCC (41).

The most common *PTCH1* mutations were frameshifts resulting in premature chain termination, which can cause premature termination of the PTCH protein (42-45). A

recent survey found that *PTCH1* had two mutated states—germinal and somatic mutation. More than 70% of patients with sporadic BCCs and xeroderma pigmentosum (XP) related BCCs detect somatic mutations of *PTCH1*, suggesting that abnormal activation of HH signaling is a precondition for both BCC associated with the GS and sporadic BCCs development (11,24,46-50).

Furthermore, a study shows that the *PTCH1* expression level was higher in BCC with both mutation types than those with only germinal mutations (51). National Cancer Institute of USA evaluated 18 NBCCS families with whole-exome sequencing and revealed that eighty-nine percent of these families expressed disease-causing mutations in *PTCH1* (52). Similarly, Undén *et al.* also identified that PTCH1 mRNA was over-expressed in BCC cells compared to the expression level in non-tumorous epidermal cells (53).

The *PTCH2* gene is a protein-coding gene located on 1p34.1. It encodes a 1203-amino acid protein (transmembrane receptors) of the patched gene family in the SHH pathway, mainly expressed in the skin and testicular epithelial cells (54). Previously, a Chinese Han family with NBCCS carrying a heterozygous germline missense mutation in *PTCH2* was reported by Fan *et al.* (55). And Fujii *et al.* reported a 13-year-old girl diagnosed with NBCCS based on multiple keratocystic odontogenic tumors and rib anomalies, who carried a frameshift mutation in the *PTCH2* gene (c.1172_1173delCT) suggested that *PTCH2* variants can also cause NBCCS, albeit with a milder phenotype (36). However, a healthy female with a *PTCH2* homozygous frameshift variant was reported, and she did not have any of the symptoms included in the diagnostic criteria for NBCCS (56). Whether *PTCH2* variants are associated with NBCCS is still unclear, as the number of cases with *PTCH2* mutations remains limited. The accumulation of such patients is expected to clarify their characteristic phenotype further.

TP53

TP53 is the second essential gene in BCC carcinogenesis. It maintains genomic stability by encoding the P53 protein that regulates the cell cycle, induces apoptosis, and activates DNA repair. Mutations of *TP53* have been identified in 20 to over 60 percent of sporadic BCCs (11). It is known that P53 is related to the early development of many different types of cancer, including BCC. And the loss of heterozygosity (LOH) of P53 appears mutually exclusive with *PTCH1* (11). Furthermore, P53 protein is involved in the aging process of keratinocytes, and a function of the protein may facilitate BCCs growth in this case (11).

Ultraviolet (UV) radiation exposure as a leading environmental agent can result in several oncogenes and anti-oncogenes mutations implicated as drivers in BCC formation (4,11,57). The pattern of genetic mutations involved in BCC pathogenesis is consistent with DNA mutations caused by ultraviolet (UVA and UVB), owing to the "UV signature" mutations they harbored (58,59). Cyclobutane dimers and pyrimidine (6–4) pyrimidone photoproducts [6-4PPs, repaired through a process known as nucleotide excision repair (NER) after damage] (60) are used for UV landmark producing (C to T or CC to TT transversions) (61,62). Within these genes, the mutational profiles of BCCs reveal evidence of UV-induced mutagenesis. In most cases, mutations identified in both the HH/Patched/SMO pathway and TP53 are consistent with UV radiation-induced mutagenesis (63), which shows that repairing UV-induced DNA damage can reduce the carcinogenicity of BCC. In addition to UV-induced changes, other factors are also linked to mutations in BCCs, such as oxidative stress (11,46).

Besides BCC-specific mutational drivers (*PTCH1*, *TP53*), there are pigmentary-traits-determined genes relevant for germline polymorphisms, including melanocortin-1 receptor (*MC1R*), the human homolog of agouti signaling protein gene (*ASIP*), and tyrosinase (*TYR*). The increased risk of BCC development is associated with single nucleotide polymorphisms, in which *ASIP* and *TYR* genes are involved and responsible for the regulation of melanin hormones (64-66).

Personal and/or family history of skin cancer, coupled with fair complexion, light/red hair color, light eye color, and poor tanning ability (high sensitivity to UV exposure), are well-known BCC risk factors (7,67-69). Pigmentation is a multigenic trait, and MC1R, a membrane G coupled protein involved in melanin production, is a major factor in determining skin and hair color (70). Several studies indicate that mutations of the *MC1R* gene are significantly associated with BCC risk and exert carcinogenic pigmentation-independent effects (65,66,71). A family history of skin cancer is closely related to an increased risk of developing BCC under 40 (odds ratio 2.49, 95% CI: 1.80–3.45), independent of the MC1R phenotype (72).

Tyrosinase, encoded by *TYR* gene, is located on the

human chromosome 11q14-q21 (73). Tyrosinase is a copper-containing enzyme and plays an important role in melanin production by catalyzing the oxidation of tyrosine to dopamine (DOPA), DOPA to L-dopaquinone, and 5,6-dihydroxyindole to 5,6-in-dolequinone in skin, hair, and eye (74). Mutations in the *TYR* gene may cause oculocutaneous albinism (OCA), a genetic disorder related to a higher risk of non-melanoma skin cancer (NMSC) (64).

Concerning multiple BCCs genetic susceptibilities, several studies have found an association between main factors, such as the number of BCCs, the vitamin D receptor, tumor necrosis factor, polymorphisms shown by the cytochrome P-450 (*CYP2D6*) and the glutathione S-transferase (*GST*) supergene family. The importance of these factors in cellular mechanisms such as metabolism and detoxification has been proved (75-78). However, the connection between these genetic polymorphisms, oncogenesis, and the clinical phenotype remains unclear.

Several pieces of research have identified genetic variants that may affect BCC risks (79-82). For example, a genome-wide association meta-analysis reveals that single nucleotide polymorphisms in genes participating in DNA excision repair may be involved in the etiopathogenesis of BCC (83).

Inherited disorders

Certain inherited disorders, including GS, XP, and Bazex-Dupré-Christol syndrome (BDCS), are considered genetic risk factors for BCC, predisposing BCC at an early age (84-86).

GS

GS is a rare multi-system disorder of autosomal dominant inheritance. In most cases, caused by germline inactivating mutations of the human *PTCH1* on the chromosome 9q22.3–q31, infrequently by mutations in the *SUFU* gene and *PTCH2*. It is distinguished by dysplasia and postnatal tumors, including odontogenic keratocysts, medulloblastoma, and multiple BCCs with an average age of 20 to 21 (36,55,87-89). The incidence of GS ranges from 1:56,000 to 1:164,000 among the general population (84).

XP

XP is a rare autosomal recessive disorder. Mutations in genes involved in repairing UV-induced DNA damage are the primary pathogenesis of XP, and mutations in *XPA*, *C*, and *V* were detected in 75% of all patients (90). Clinical features include early-onset pigmented skin changes and the early development of skin cancers. According to a 39-year follow-up study of 106 XP patients conducted by the National Institutes of Health (NIH, USA), 69 (65%) patients with skin cancer have a higher risk of suffering from NMSC and melanoma than the general population. Moreover, the median age at first diagnosis of NMSC was significantly younger than melanoma (91).

Bazex-Dupré-Christol syndrome

This syndrome is an X-linked dominant disorder characterized by congenital hypotrichosis, follicular atrophoderma, and multiple BCCs (92). It may be accompanied by milia, ichthyosis, neurological symptoms, and visceral malignancies (93). According to the latest research, the BDCS gene is localized on the Xq25-27.1 and yet unspecified.

Rombo syndrome

In 1981, Michaëlsson *et al.* (88) described Rombo syndrome for the first time. An autosomal dominant inheritance across at least four generations was detected, leading to early-onset and frequent BCCs in the middle of the nineteen-thirties. This syndrome is characterized by dilation of the peripheral blood vessels with cyanosis and skin follicle atrophy features, which can be seen in the first decade of life. Dilation of the capillaries and milia-like papules on the face are particularly prominent in adults; eyelash and eyebrow loss or abnormalities, as well as less common capillary hemangiomas, were also observed. Histological analysis revealed regional loss of elastin clumps and elastin.

OCA

OCA is a group of autosomal recessive disorders. It manifests as a series of visual impairments and hypopigmentation of the skin and hair due to impaired melanin biosynthesis. There is an increased risk of early-onset skin cancer in those with OCA. OCA is caused by mutations in genes encoding proteins involved in the melanin biosynthesis pathway, which include melanogenic enzymes [i.e., TYR, tyrosinase-related protein 1 (*TYRP1*)] and specific transport proteins found in melanosomes (64). The TYR enzyme catalyzes the

first step in melanin biosynthesis by oxidizing L-tyrosine to DOPA (dihydroxy-L-phenylalanine). In patients with OCA, squamous cell carcinoma is the most prevalent cancer type that arises; BCC and melanoma also occur (94). Malignant melanoma (MM) is considered rare in patients with OCA compared to NMSC (95).

Other genes

BRCA1 and BRCA2

BRCA1 and *BRCA2* are tumor suppressor genes encoding proteins that help repair damaged DNA. Specific mutations of these genes may increase breast and ovarian cancer risks and also lead to several additional types of cancer.

BRCA1 mutations confer a predisposition to various cancer types, including melanomas, mesotheliomas, clear cell renal cancer, and BCCs (96-98). And a study has proved that *BRCA2* can increase the risk of BCCs (99). Hence, more careful skin surveillance and photoprotection should be promoted for patients with the cancers mentioned above and/or known carriers of *BRCA1* and *BRCA2*.

CTLA-4

Specific genes such as *CTLA-4*, which can affect the immune response, may also influence BCC predisposition. *CTLA-4* is a protein-coding gene that delivers suppressive signals to regulatory T cells and is associated with the immune tolerance induced by UV light. In a case-control study, genetic mutations of *CTLA-4* affect the risk of developing BCC, particularly in those with a high frequency of severe tanning (100). In addition, *CTLA-4* polymorphism (rs5742909) has been reported that may influence the susceptibility to multiple BCCs (101).

AS3MT

According to multiple studies, chronic arsenic exposure may cause superficial multicentric BCC (102-106) and the intake of arsenic mostly from contaminated drinking water, seafood, or medications. Some genetic factors related may affect BCC risks, such as *AS3MT* [arsenic (+3 oxidation state) methyltransferase gene, the major arsenic-metabolizing gene] mutation (107,108). *AS3MT* is a protein-coding gene encoding the arsenite methyltransferase enzyme and telomere length (105,109). A detailed study conducted by Srinivas *et al.* investigates the effect of telomere length on the disease risk. The result shows that compared with 533 healthy controls, the telomere length of 528 BCC-combined arsenic-exposed cases significantly decreased, which indicates that with arsenic exposure, decreased telomere length of individuals raises the risk of developing BCC. And there was a synergistic effect in those with the highest arsenic exposure and the shortest telomeres (109).

It should be noticed that beyond the genes mentioned above (*Table 2*), other tumor-related genes and pathways are also involved in the pathogenesis of BCC (11,46,63,94,121).

A genetic analysis study of 293 BCCs concluded that gene mutations of eighty-five percent cases were related to the HH pathway (*PTCH1* 73%, or *SMO* 20%, and *SUFU* 8 %) and *TP53* (61%) (46). Furthermore, additional driver mutations in other cancer-related genes, such as *MYCN* (30%), *PTPN14* (23%), *PPP6C* (15%), *STK19* (10%), *LATS1* (8%), can also be observed in 85% of cases. The up-regulation of N-Myc and Hippo-YAP pathway target genes (*MYCN*, *PTPN14*, and *LATS1*) shows the potential relevance in BCC tumorigenesis and progression (46). These factors are likely to account for the enormous phenotypic and biological variation in BCC. In a study of 12 sporadic BCCs and normal skin, mutations were identified in several known or presumptive cancer genes (*CSMD1*, *DPP10*, *NOTCH1*, and *PREX2*) via whole-exome sequencing; meanwhile, mutational hotspots were detected in *STAT5B*, *CRNKL1*, and *NEBL* (63). The relevance of these mutations to the genesis of BCC, however, is still unclear. Recently, Sławińska *et al.* reported that *STAT3* and *IL-6* polymorphism are associated with the risk of BCC (122).

Conclusions

The hereditary basis of BCCs can vary from targeted mutations in the HH signaling pathway to deficiencies of tumor suppressors and melanin synthesis. These may lead to DNA damage and promotes BCC growth. The knowledge and characterization of the BCC genetic factors could underlie the development of new therapies and ultimately reduce BCC's worldwide burden.

Table 2 Frequency of mutations and LOH in cancer-related genes across published studies in BCC

Gene	No. of samples analyzed	Mutations (%)	LOH (%)	Year	References
PTCH 1	37	32.4	24.3	1996	(50)
	24	54.2	Na	1996	(14)
	55	Na	66.7	1996	(110)
	26	11.8	38.2	1998	(45)
	15	40	53.3	2002	(111)
	14	64.3	92.8	2005	(112)
	12	75	41.7	2005	(24)
	12	8.3	40	2011	(113)
	31	54.8	43.5	2013	(114)
	42	66.7	52.6	2014	(63)
	293	73	55	2016	(46)
	20	60	10	2019	(51)
	191	58.6	23	2020	(115)
	14	50	Na	1992	(116)
	27	56	Na	1993	(117)
TP53	18	61.1	5.5	1996	(110)
	24	45.8	Na	1996	(14)
	20	35	Na	1999	(118)
	15	33	Na	2002	(111)
	148	47.3	Na	2003	(119)
	42	40.5	7.9	2005	(24)
	30	20	Na	2014	(120)
	12	66.7	Na	2014	(63)
	293	61	17	2016	(46)
	191	31.4	Na	2020	(115)
SMO	47	6.38	Na	1998	(25)
	42	9.5	Na	2005	(24)
	293	20	Na	2016	(46)
SUFU	42	2.4	Na	2005	(24)
	293	8	5	2016	(46)

LOH, loss of heterozygosity; BCC, basal cell carcinoma; Na, not applicable.

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Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Frontiers of Oral and Maxillofacial Medicine* for the series "Diagnosis and Treatment of Periorbital Basal Cell Carcinoma". The article has undergone external peer review.

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://fomm.amegroups.com/article/view/10.21037/fomm-21-70/rc

Peer Review File: Available at https://fomm.amegroups.com/article/view/10.21037/fomm-21-70/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://fomm.amegroups.com/article/view/10.21037/fomm-21-70/coif). The series "Diagnosis and Treatment of Periorbital Basal Cell Carcinoma" was commissioned by the editorial office without any funding or sponsorship. LMH and VK served as the unpaid Guest Editors of the special series. LMH serves as an unpaid editorial board member of *Frontiers of Oral and Maxillofacial Medicine* from September 2020 to August 2022. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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