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Exploration of the causative gene in a case of multiple nevoid basal cell carcinoma: A case report

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Abstract

Nevoid basal cell carcinoma syndrome is a rare autosomal dominant disorder characterized by a diverse clinical presentation, which includes developmental abnormalities and tumorigenesis that can impact multiple organ systems. Basal cell carcinoma is the most common and characteristic clinical presentation in patients with NBCCS. There are three identified causative genes for this disease, the PTCH1 gene located at 9q22-31, the PTCH2 gene at 1p32-34, and the SUFU gene at 10q24.32. In this paper, we report a case of multiple nevoid basal cell carcinoma. The mutated gene in this patient was determined to be the ELP1 gene located on chromosome 9. This patient's ELP1 gene mutation may contribute to the development of multiple nevoid basal cell carcinomas on the face.

Keywords

Multiple nevoid basal cell carcinoma, nevoid basal cell carcinoma syndrome, basal cell nevus syndrome, Gorlin syndrome, Gorlin–Goltz syndrome, ELP1 gene, skin cancer

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Background

Nevoid basal cell carcinoma syndrome (NBCCS), also known as basal cell nevus syndrome (BCNS), Gorlin syndrome, and Gorlin–Goltz syndrome, was first described by Gorlin and Goltz in 1960.[1] NBCCS is a clinically rare autosomal dominant disorder. There are three identified causative genes associated with this disease, the PTCH1 gene located at 9q22-31, the PTCH2 gene at 1p32-34, and the SUFU gene at 10q24.32. The probability of detecting mutations in the PTCH1, PTCH2 or SUFU genes in patients with NBCCS was 88.1%, 1.2%, 1.2%.[2]

The clinical manifestations of NBCCS are diverse and commonly include basal cell carcinoma, multiple odontogenic keratocysts, central nervous system damage, and skeletal deformities. Basal cell carcinoma is the most common and characteristic clinical presentation in patients with NBCCS.

The First International Colloquium on Basal Cell Nevus Syndrome in 2011 proposed the following diagnostic criteria[3]:

The diagnostic criteria for NBCCS include six major criteria and seven minor criteria.

Clinical confirmation of the diagnosis of NBCCS requires compliance: (1) one major criterion and molecular confirmation; (2) two major criteria; or (3) one major and two minor criteria.

The molecular confirmation of clinically common genes is PTCH1, PTCH2, and SUFU.

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The major criteria for diagnosis would include (1) basal cell carcinoma before 20 years old or excessive numbers of basal cell carcinomas out of proportion to prior sun exposure and skin type; (2) keratocystic odontogenic tumor before 20 years of age; (3) palmar or plantar pitting; (4) lamellar calcification of the falx cerebri; (5) medulloblastoma, typically desmoplastic; (6) first degree relative with NBCCS.

The minor criteria would include: (1) rib anomalies; (2) other specific skeletal malformations and radiologic changes (i.e., vertebral anomolies, kyphoscoliosis, short fourth metacarpals, postaxial polydactyly); (3) macrocephaly; (4) cleft lip or palate; (5) ovarian or cardiac fibroma; (6) lymphomesenteric cysts; (7) ocular abnormalities (i.e., strabismus, hypertelorism, congenital cataracts, glaucoma, coloboma).

Case Presentation

The patient is a 43-year-old female. Her mother is deceased, but her father, sister, and daughter are alive and exhibit similar facial skin lesions. The patient first visited the Cosmetic Plastic Surgery Clinic at the Affiliated Hospital of Qingdao University in March 2014 for treatment due to "multiple nevoid skin lesions on the face for 34 years". As shown in Figure 1, in this treatment, the patient underwent surgical excision of multiple skin lesions located on the right lower eyelid, the right lateral canthus, the right cheek, the right side of the lower edge of the nasal septum, the left cheek, and the left lower eyelid. After the surgery, three skin lesions located on the left lower eyelid, right lateral canthus, and right cheek were sent to the Department of Pathology for histopathological examination. The pathology report showed that all three skin lesions were "basal cell carcinoma".

In April 2014, the patient went back to our clinic for further treatment of other skin lesions on the face. After excluding contraindications to surgery, a total of four skin lesions located on the scalp, left cheek, left nasal flank, and left medial canthus were surgically excised. After the surgery, four skin lesions were sent for frozen section examination, and all were diagnosed as "basal cell carcinoma". The postoperative histopathological results were shown in Figure 2.

In November 2016, the patient came back to our department seeking treatment for "skin lesions on the right nasal flank for more than 6 years with rapid growth for 3 years". After exclusion of contraindications to surgery, the

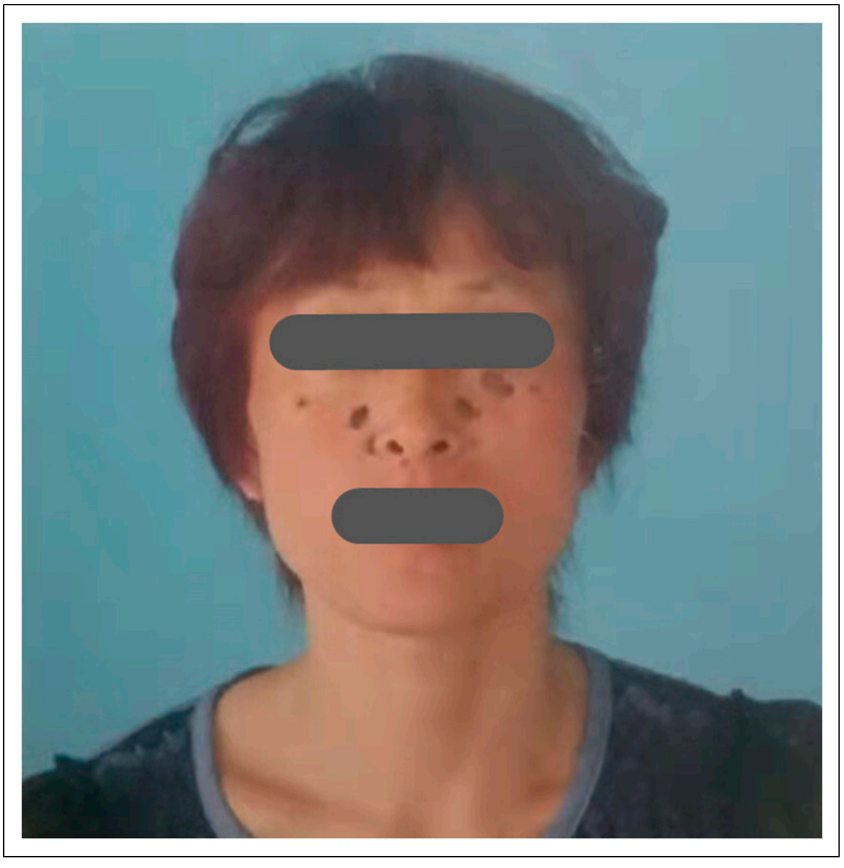

Figure 1. The preoperative anteroposterior photograph of the patient's head and face.

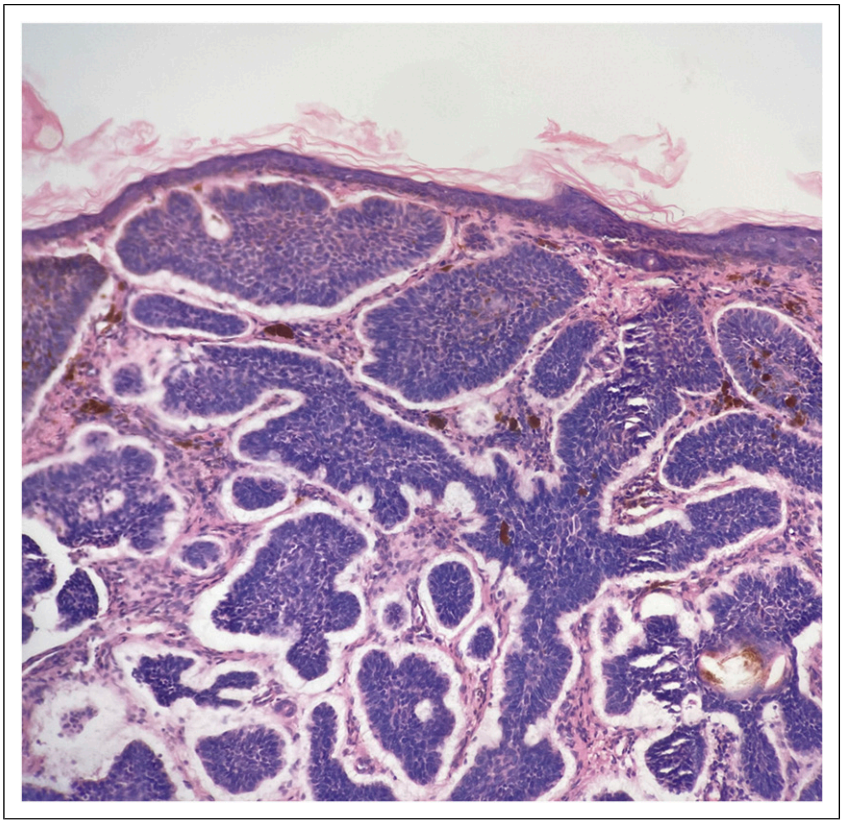

Figure 2. Postoperative pathology (HE staining showing basal cell carcinoma).

patient underwent surgical treatment. A total of five skin lesions located on the right nasal flank, right forehead, right eyebrow, left lower eyelid, and left upper lip were removed during surgery. The recovery effect of the patient's surgical area is shown in Figure 3. After the surgery, five skin lesions were sent for frozen section examination, and all were diagnosed as "basal cell carcinoma".

In the past few years, the patient has been followed up in our clinic. Due to the cost of surgery, the patient's new nevoid lesions growths on her face have been treated with laser therapy for several years. In 2022 the patient came to our clinic for a follow-up visit. During this visit, the patient described multiple new nevoid lesions on her daughter's face. She also raised important questions and expressed a strong desire to learn more about her condition. Additionally, she conveyed her wish to explore treatment options that could halt the progression of her daughter's illness.

The relevant diagnostic basis for this patient: (1) The patient has more than 2 basal cell carcinomas. (2) The patient's first-degree relative (the patient's father) had more than 2 nevoid basal cell carcinomas confirmed by pathologic diagnosis. (3) Multiple relatives in the family have facial nevoid lesions.

Accordingly, we hypothesized that the patient might have nevoid basal cell carcinoma syndrome. To further clarify the diagnosis, we collected whole blood samples from the patient and sent it to the medical laboratory of BGI in Shenzhen for whole exome sequencing. The detection area is the exon regions of approximately 20,000 genes in the human genome and mitochondrial genome. The detection strategy is to detect genes with a clear pathogenic relationship in the OMIM database in response to the patient's claims. The detection method is Chip Capture High-Throughput Sequencing. The detection results are shown in Table 1.

Whole exome sequencing testing in this patient reported the mutated gene to be the ELP1 gene located on chromosome 9, unlike the three causative genes that have been identified in NBCCS.

Discussion

Elongator is a protein complex that plays an important role in RNA transcription and translation. The Elongator complex consists of six subunits including ELP1, ELP2, ELP3, ELP4, ELP5 and ELP6.[4] The main role of the complex is to facilitate nucleotide addition in RNA transcription and translation, thus contributing to the movement of RNA polymerase and ribosomes. The Elongator complex has also been implicated in processes such as the cell cycle,

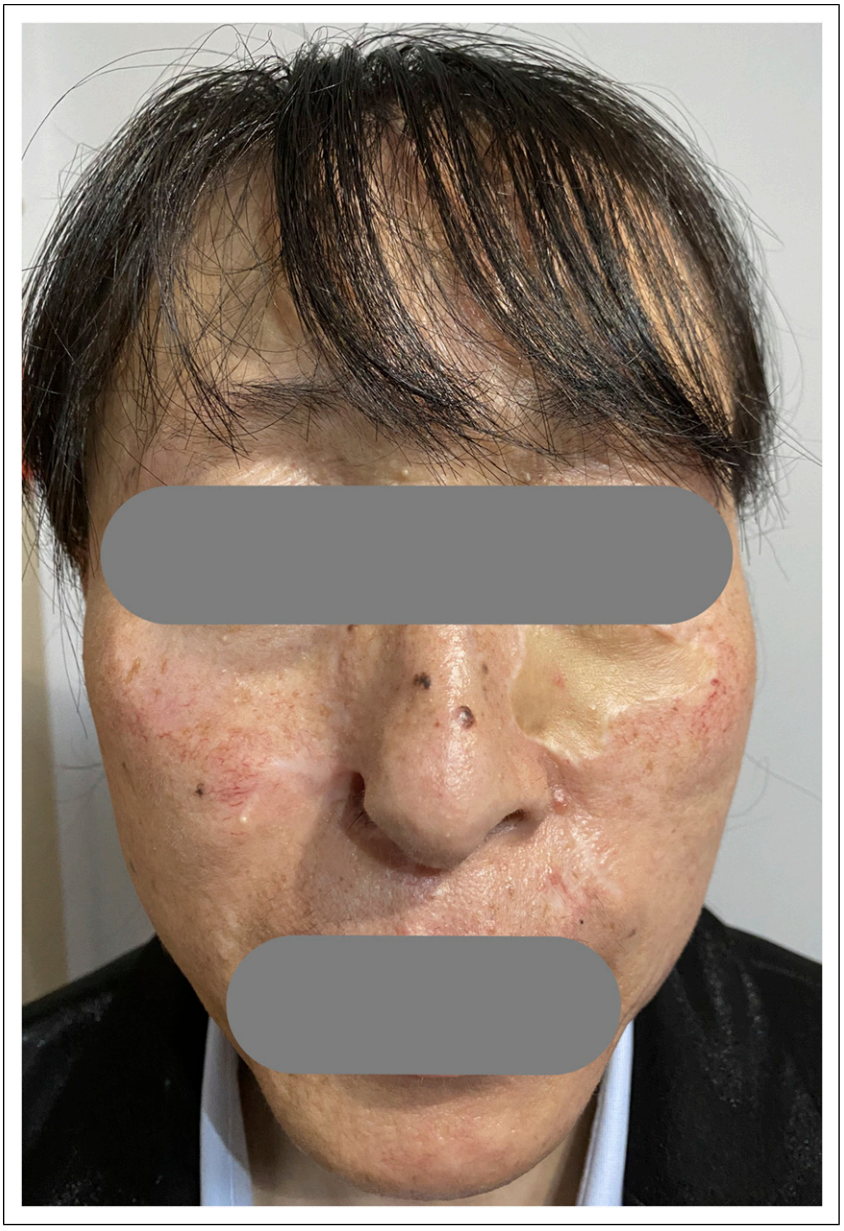

Figure 3. The anteroposterior photograph of the patient's head and face following multiple surgeries.

protein translation, and cell apoptosis. It has been shown that the function of ELP1 is related to cytoskeletal emesis, cytoskeletal organization, axonal transport, and cell adhesion and migration.[5] Current studies on the ELP1 gene are based on medulloblastoma and hereditary sensory and autonomic neuropathies. Deletion of the ELP1 gene leads to the death of mouse embryos.[6] ELP1 plays a role in neurogenesis, neuronal survival, and peripheral tissue innervation. A group of genes involved in myelin formation require ELP1 for efficient transcription. The ELP1 gene has not been previously reported to be associated with the development of basal cell carcinoma.

In terms of the treatment of NBCCS, for this case we focus on the treatment of basal cell carcinoma of the skin. Once basal cell carcinoma is detected, we recommend radical treatment. The most common form of treatment is surgical removal of the diseased area. The preoperative design of surgical treatment is very important. First, it is important to ensure complete eradication of the basal cell carcinoma. Secondly, it is important to preserve as much normal tissue as possible and minimize scar formation to prevent disfigurement. Mohs Micrographic Surgery achieves favorable results in clinical treatment.[7] Because scarring often occurs

Table 1. Whole exome sequencing results (BGI, Shenzhen, China).

Detection conclusion
Main detection results:
No clinically unknown variation consistent with the pathogenic/suspected pathogenic variation/genetic pattern associated with the clinical phenotype of the subject was detected
Secondary detection results:
The ELP1 gene associated with inherited sensory and autonomic neuropathy type 3 / medulloblastoma (ELP1 gene related) detected an unknown variation associated with the phenotype of the subject
Mitochondrial gene detection results:
No mitochondrial gene variation associated with clinical phenotype was detected
Unexpected detection results:
No unexpected pathogenic or suspected pathogenic variants detected (SecondaryFinding_Var database)

Secondary detection results							
Number	Gene	Chromosome position	Transcription number nucleotide change (amino acid change)	Gene subregion	Genotype	Pathogenicity classification	Related diseases/ genetic patterns
1	ELP1	Chr9: 111658826	NM_003640.3: c.2686G>A (p.Gly896Ser)	EX25/ CDS24	Heterozygote	Unknown	Hereditary sensory and autonomic neuropathy type 3 (OMIM: 223900) /AR medulloblastoma (ELP1 gene related) (OMIM:155255)/ AD,AR,SMu

after the surgical removal of a lesion, patients may be hesitant to undergo surgery, particularly if the lesion is located on the face. In addition to surgical treatments, we can also use cryotherapy, laser therapy, photodynamic therapy, and medication. It is particularly emphasized that radiotherapy is contraindicated in patients with NBCCS and carries a potential risk of cancer. Therefore radiotherapy should be avoided or very low doses of radiation should be used whenever possible.[8] Drugs known to be therapeutically effective include imiquimod 5%,[9] etretinate,[10] 5-fluorouracil,[11] capecitabine,[12] and Hedgehog inhibitors, etc. Hedgehog inhibitors including Vismodegib and Sonidegib.[13]

Conclusions

The mutated gene in this patient was the ELP1 gene located on chromosome 9, which is different from the three disease-causing genes that have been identified. We speculate that this mutated gene possibly causative multiple nevoid basal cell carcinoma of the face. We further speculate that all relatives in this patient's family with facial nevoid lesions have this mutated gene. Next, we plan to conduct genetic studies on other relatives in the family with the same phenotype.

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Author contributions

All authors have read and approved the final manuscript. LYT, CLJ, and CX have made substantial contributions to the conception design, or acquisition of the data. LYT were involved in the data analysis and interpretation and drafted the manuscript. GXJ, RJZ, and MYX have been involved in revising it critically for important intellectual content.

Declaration of conflicting interests

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Contributorship

Yutong Liu wrote the first draft of the manuscript. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

Ethical statements

Ethics approval

Ethical approval to report this cas was obtained from *Ethics Committee of Affiliated Hospital of Qingdao University (QYFY WZLL 28898)*.

Consent to participate

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Consent for publication

Written informed consent was obtained from the patient for the anonymized information to be published in this article.

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Data availability statement

The data are available from the corresponding author on reasonable request.

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