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CASE REPORT

# A novel splicing mutation of *PTCH1* in a Chinese family with nevoid basal cell carcinoma syndrome

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**Abstract**
Nevoid basal cell carcinoma syndrome (NBCCS) is a rare autosomal dominant disease characterized by the development of multiple jaw keratocysts and basal cell carcinomas (BCC) and accompanied by diverse phenotypes. The establishment of diagnosis lies on the identification of a heterozygous germline pathogenic variant in the patched homolog 1 gene (*PTCH1*). *PTCH1* has alternative splicing and selective initial coding exon, leading to three types of encoding proteins (PTCHL, PTCHM and PTCHS). The expression of each protein in NBCCS remains ambiguous, especially the importance of the first two exons in translation. Here, we report a Chinese NBCCS family of a novel *PTCH1* heterozygous mutation (IVS 2, c.394+1G>T, g.10652G>T) identified by genomic sequencing and reverse-transcription-PCR as aberrant splicing. To the best of our knowledge, this is the first report of NBCCS with a splicing site mutation in intron 2 resulting in exon 2 skipping. Our finding suggests that exon 2 plays an important role in the development of NBCCS and further speculates that the role of longer isoforms PTCHL and PTCHM is crucial in NBCCS, while that of short isoform PTCHS might be dispensable.

**Keywords** Nevoid basal cell carcinoma syndrome · *PTCH1* gene · Novel mutation · Aberrant splicing · Exon skipping

## Introduction

Nevoid basal cell carcinoma syndrome (NBCCS), also known as Gorlin syndrome, is a rare autosomal dominant disease characterized by the development of multiple jaw keratocysts and basal cell carcinomas (BCC) and accompanied by various phenotypes, such as macrocephaly, frontal bossing, bifid ribs, wedge-shaped vertebrae, and ectopic calcification [1]. The establishment of diagnosis lies in the identification of a heterozygous germline pathogenic variant in the patched homolog 1 gene (*PTCH1*) [2]. *PTCH1* has alternative splicing and selective initial coding exon, leading to five different isoforms and three corresponding encoding proteins [3]. The function of each protein isoform in the development of NBCCS remains unclear. We present a Chinese NBCCS family of a novel *PTCH1* mutation identified by genomic sequencing and reverse-transcription-PCR as aberrant splicing in the selective initial coding region.

## Case report

A 46-year-old man was admitted to the ophthalmology department with a medical history of eyelid BCC for 17 years and meibomian gland carcinomas for 5 years. Upon physical examination, he showed multiple black papules involving the face and neck with partial epithelium scabs (Fig. 1a). The dermal pathology revealed superficial BCC (Fig. 1b). The family investigation indicated his deceased mother and elder brother had similar symptoms (Fig. 2a). The patient was clinically diagnosed with NBCCS according to Evans' criteria [4].

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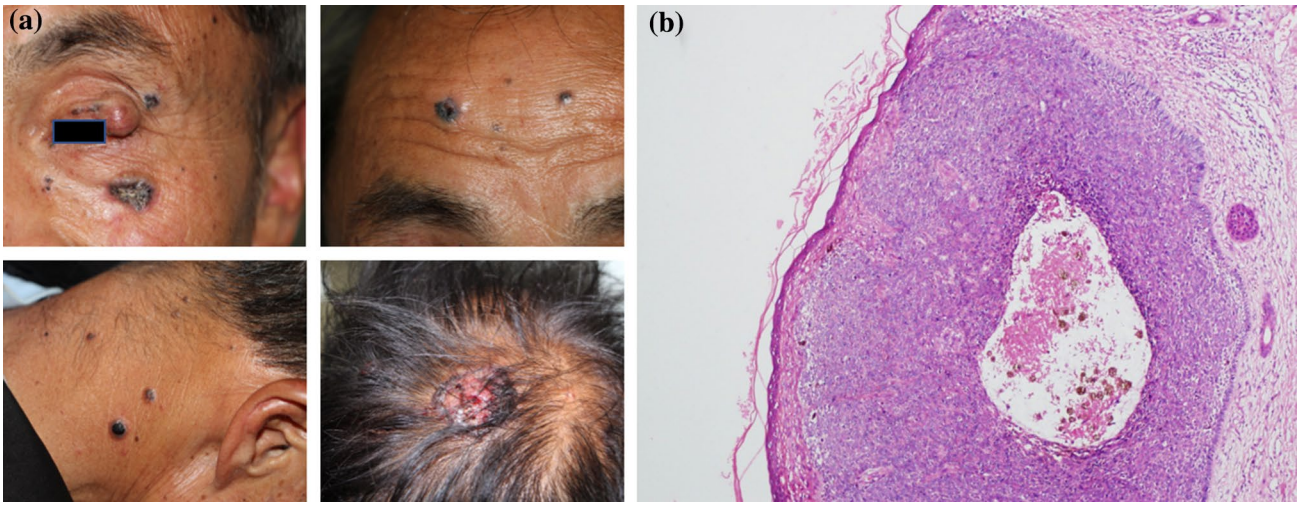


**Fig. 1** Clinical features of the patient. **a** Multiple black papules in the head and neck region with partial epithelium scabs. **b** HE staining of skin tissue revealed superficial basal cell carcinoma (×100)

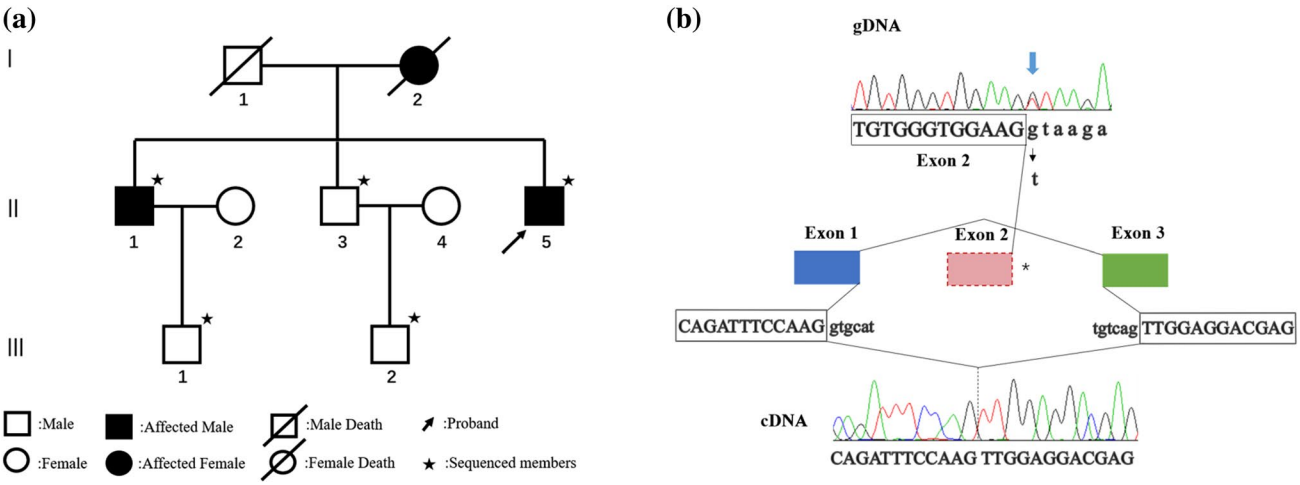


**Fig. 2** Genetic features of the patient. **a** Pedigree of the family. **b** Location of mutation in *PTCH1* gene and its splicing consequence. Sanger sequence revealed a nucleotide change c. 394+1G>T in the splice donor site of intron 2 (arrow). Boxes indicate exons. Asterisks indicate the positions of mutations. Reverse-transcription-PCR revealed the exon 2 skipping

Gene analysis using peripheral blood was performed in five available family members by direct sequencing. A novel *PTCH1* heterozygous mutation (c.394+1G>T, g.10652G>T) in the splice donor site of intron 2 was identified in both the patient and his affected brother (as per Genbank entry NM_000264.4, transcript 1b). The abnormal splicing patterns were predicted by Human Splicing Finder as donor site alteration affecting splicing. mRNA of the patient was obtained to establish reverse-transcription-PCR, which revealed the exon 2 skipping (Fig. 2b). The mutation was interpreted as pathogenic variant according to the American College of Medical Genetics and Genomics guidelines [5]. The results verified the genotypes co-segregated with phenotypes in this pedigree. Thus, the patient was genetically diagnosed with NBCCS.

## Discussion

*PTCH1* maps at 9q22.32 contain 23 coding exons and encode a protein containing 1447 amino-acid residues including 12 transmembrane-spanning domains. So far, there exist five first exon versions (1a, 1b, 1c, 1d, and 1e), resulting in three different length protein isoforms called PTCHL, PTCHM, and PTCHS. Different isoforms are distinguished in which protein isoform PTCHL (translate from 1b) contains unique

amino acid N-terminal sequence, which is missing in protein isoform PTCHM (1a) and protein isoform PTCHS (1c, 1d, and 1e) [6]. Moreover, isoform PTCHS also lacks the entire N-terminus and the first transmembrane region. Above all, translations of PTCHL and PTCHM start at the first exon, respectively, exon1b and exon 1a, whereas the translation of PTCHS starts at the third exon [7]. According to previous studies, NBCCS is suggested to develop because of haploinsufficiency of PTCHL and PTCHM but not PTCHS [7, 8]. A recent study also put forward the opinion that *PTCH1* isoform 1b (PTCHL protein) was a major transcript in the development of NBCCS, which reminds the indispensability of the first two exons [6]. The most common mutations in *PTCH1* were missense and frameshift mutations [9]. There have been few cases with *PTCH1* splicing mutations in the first two exons reported thus far. A study of splicing mutations in *PTCH1* considered them to be inclined to localize in splice donor site [10]. Here, we present a patient carrying a splicing mutation in the splice donor site of intron 2. This mutation is located downstream of the initiation codon used for the translation of PTCHL and PTCHM, but upstream of PTCHS production. Therefore, our study conforms to the opinion that PTCHS was less important in NBCCS. To the best of our knowledge, this is the first report of NBCCS with splicing site mutation in intron 2 resulting in exon 2 skipping.

Our finding enriches the *PTCH1* gene mutation database and concludes that exon 2 plays a critical role in the development of NBCCS. Therefore, we speculate that the role of longer isoforms PTCHL and PTCHM is crucial in NBCCS, while that of short isoform PTCHS might be dispensable. Furthermore, the function of different isoforms may need advanced research.

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## Compliance with ethical standards

**Conflict of interest** The authors declare no conflict of interest.

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