CASE REPORT

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Odontogenic keratocysts are an important clue for diagnosing basal cell nevus syndrome

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ABSTRACT

Basal cell nevus syndrome (BCNS) is an autosomal dominant skin disorder characterized by multiple basal cell nevi. Patients with BCNS tend to develop basal cell carcinoma (BCC) and frequently show skeletal abnormalities. Most cases of BCNS are caused by mutations in patched 1 (*PTCH1*). *PTCH1* encodes a transmembrane receptor protein for the secreted molecule sonic hedgehog, which plays a key role in the development of animals ranging from insects to mammals. We analyzed two Japanese BCNS patients from two independent families. Both of our patients had multiple jaw keratocysts. In one patient, these were the key to noticing his BCNS, as he had no skin tumors. The early detection of *PTCH1* mutations would enable BCNS patients to be carefully followed up for the occurrence of BCC. The diagnosis of BCC at the early stage leads to prompt surgical treatments, resulting in a good prognosis. The present cases suggest that keratocysts of the jaw might be an important clue for diagnosing BCNS.

Keywords: basal cell nevus syndrome, mutation, PTCH1

Abbreviations:
BCC: basal cell carcinoma
BCNS: basal cell nevus syndrome
PTCH1: patched homologue 1

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INTRODUCTION

Basal cell nevus syndrome (BCNS, OMIM#109400) is an autosomal dominant skin disorder characterized by multiple basal cell nevi.[1] Patients with BCNS tend to develop basal cell carcinoma (BCC) and frequently show skeletal abnormalities. Most cases of BCNS are caused by mutations in patched 1 (*PTCH1*), which is located at chromosome 9q22.3.[2] *PTCH1* encodes a transmembrane receptor protein for the secreted molecule sonic hedgehog, which plays a key

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role in the development of animals ranging from insects to mammals.[3]

We analyzed two Japanese BCNS patients from two independent families who presented or were referred to our department. The clinical features of each patient are detailed below. Following informed consent and in accordance with the Declaration of Helsinki principles, genomic DNA from the participants was used for whole-exome sequencing analysis, using methodology described elsewhere.[4]

CASE REPORT

Patient 1

A man in his 30s presented with odontogenic keratocysts of the jaw (Fig. 1A). He had first visited a dentist and a keratocyst was found on his upper jaw. He had had another keratocyst of his lower jaw before. His mother and brother also had keratocysts of the jaw. BCNS was suspected, and the patient was referred to our department. He had no skin tumors suggestive of basal cell nevus. Magnetic resonance images showed lamellar calcification of the falx cerebri. He had rib anomalies. Whole-exome sequencing revealed a previously reported[5] heterozygous deletion mutation, c.2798delC (p.Ala933fs*29), in *PTCH1*.

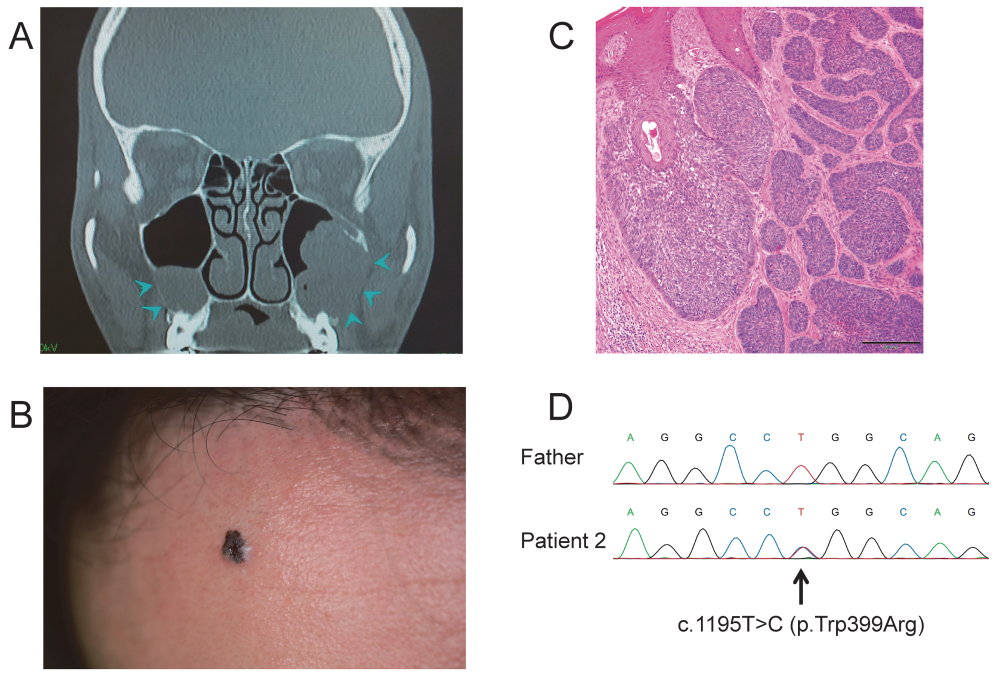

Fig. 1 Clinicopathological features of the two BCNS patients and the causative *PTCH1* mutation in Patient 2

Fig. 1A: A computed tomography coronal section of Patient 1. Jaw keratocysts are shown by the sky blue arrowheads.

Fig. 1B: The clinical features of a BCC lesion on the forehead of Patient 2. A pearl-like fringe surrounds a central crater.

Fig. 1C: The BCC on the forehead of Patient 2 histopathologically consists of multiple nests of basaloid tumor cells in the superficial dermis. Scale bar: 100μm.

Fig. 1D: In Patient 2, a novel heterozygous missense mutation, c.1195T>C (p.Trp399Arg), in *PTCH1* is shown by Sanger sequencing.

Patient 2

A 38-year-old man presented with multiple BCC (Fig. 1B, C). He first presented with a blackish nodule on his forehead. A clinical examination revealed many blackish lesions on his head, and the diagnosis was multiple BCC. He had odontogenic keratocysts of the jaw. No member of his family had any similar symptoms. Magnetic resonance images showed lamellar calcification of the falx cerebri. He had a cleft lip at birth, which is a minor criterion for BCNS. Whole-exome sequencing revealed a previously unreported heterozygous *PTCH1* mutation, c.1195T>C (p.Trp399Arg). We confirmed its presence in genomic DNA by Sanger sequencing and demonstrated its absence in parental genomic DNA. The mutation was considered to be *de novo* (Fig. 1D). This missense mutation was predicted to be disease causing by the Mutation Taster in silico bioanalysis tool and to be probably damaging by PolyPhen-2.

DISCUSSION

To confirm the diagnosis of BCNS, the presence of 2 major or 1 major and 2 minor criteria is needed.[6] Patient 1 has 3 major criteria: odontogenic keratocysts of the jaw proven by histology, lamellar calcification of the falx cerebri and rib anomalies (Table 1). Patient 2 has three major criteria and one minor criterion: more than two BCCs, odontogenic keratocysts of the jaw proven by histology and lamellar calcification of the falx cerebri; and cleft lips, respectively (Table 1).

The following facts support the pathogenicity of the present previously unreported mutation (p.Trp399Arg) in Patient 2. The mutation was absent in both parents, suggesting that it is a *de novo* condition. In addition, the mutation has not been described in the gnomAD database (https://gnomad.broadinstitute.org/) or the 1000G database (https://www.internationalgenome.org/). Moreover, several protein function prediction browsers gave a very high pathogenicity score to the mutation. Thus, according to the ACMG guideline 2015,[7] p.Trp399Arg was decided to be likely pathogenic.

Among BCNS patients with *PTCH1* mutations, most causative *PTCH1* mutations have been reported only one family and have been scattered throughout the coding regions of *PTCH1* (The Human Gene Mutation Database; http://www.hgmd.cf.ac.uk/ac/gene.php?gene=PTCH1). No apparent mutation hot spot has been reported so far. Musani et al suggested that a deletion mutation, c.3364_3365delAT (p.Met1122Valfs*22), might be a potential mutation hot spot because the mutation was reported four independent families from distant geographical areas.[8] However, the present *de novo* mutation, p.Trp399Arg, is located far from the potential mutation hot spot and is not in any mutation hot spot area in *PTCH1*.

Table 1 Detailed clinical characteristics and causative *PTCH1* mutations in each patient

Clinical or genetic feature	Patient 1	Patient 2
More than two BCCs	Not detected	+
Odontogenic keratocysts of the jaw	+	+
Lamellar calcification of the falx cerebri	+	+
Rib anomalies	+	Not detected
Mutations in *PTCH1*	c.2798delC (p.Ala933fs*29)	c.1195T>C (p.Trp399Arg)

BCC: basal cell carcinoma

Most BCNS patients are known to have jaw keratocysts. About 90% of BCNS patients present multiple jaw keratocysts, and they often develop jaw keratocysts in their teenage years.[9] The first medical visit is often to a dentist because of discomfort or infection in the oral cavity. Both of our patients had multiple jaw keratocysts. In Patient 1, these were the key to noticing his BCNS, as he had no skin tumors. The early detection of *PTCH1* mutations would enable BCNS patients to be carefully followed up for the occurrence of BCC. The diagnosis of BCC at the early stage leads to prompt surgical treatments, resulting in a good prognosis.

CONCLUSIONS

In conclusion, this study has expanded the spectrum of *PTCH1* mutations in BCNS. Furthermore, both of the present patients had keratocysts of the jaw, and the present cases suggest that keratocysts of the jaw might be an important clue for diagnosing BCNS.

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CONFLICTS OF INTEREST

None to declare.

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