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(Letter to the Editor)

A Novel Germ-line Mutation of *PTCH1* Gene in a Japanese Family of Nevoid Basal Cell Carcinoma Syndrome: Are the palmoplantar pits associated with true basal cell carcinoma?

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Nevoid basal cell carcinoma syndrome (NBCCS) is an autosomal-dominantly inherited disorder represented by multiple tumors including basal cell carcinomas (BCC) or other tumors, palmoplantar pits, odontogenic cysts and other skeletal malformations (1). Especially, medulloblastoma is the most important complication determining prognosis in early life. Recently, *PTCH1* gene was shown to be responsible for NBCCS (2,3). We describe a familial case of NBCCS with a novel missense-mutation. In addition, we investigated the expression of Ber-EP4, a marker of BCC (4) in the epidermis and the basaloid nests beneath palmoplantar pits.

Case 1 was a 47-year-old Japanese female with history of recurrent/multiple jaw cysts, who showed many tiny pits on her palms (Figure A left). Frontal bossing, mild hypertelorism and lower rib-fusion were also noted. Computed tomography revealed calcification of the falx cerebri. Neither mental retardation nor basal cell carcinomas were detected. Cases 2-4 were her 22-year-old son, 19-year-old daughter, and 17-year-old son, respectively. They also had palmoplantar pits, facial anomalies and multiple jaw cysts. Calcifications of the falx cerebri were noted in case 2 and 3, but not in case 4. Histopathology of the jaw cysts identified odontogenic keratocysts. Case 3 had a history of epilepsy in her childhood, but neither mental retardation nor BCC were detected in all 4 cases. A palmar pit from case 1 was biopsied, and the histopathological

examination showed a focal defect of the horny layer (Figure A right). There were no obvious basaloid cell nests under the lesion. The pedigree of this family is shown in Figure B. Her elder brother had also been operated for the jaw cysts and her father had a history of unidentified skin cancer. Mutation analysis was performed using SSCP followed by direct sequencing as previously reported (5), which revealed a novel mutation, C3200T, replacing threonine with isoleucine at 1067th codon on the 23rd exon of *PTCH1* gene (NM_001083602) (Figure C). The 1067th threonine is preserved between humans and *C. elegans* (Figure C). This was not detected in case 1's healthy elder sister or other healthy adults. The mutation of this family has not been described before or in the database of *PTCH1* (http://www.cybergene.se/cgi-bin/w3-msql/ptchbase/index.html).

Palmoplantar pits are occasionally associated with basaloid cell nests which are indistinguishable from BCC. They are observed only in early life (6, 7) with little malignant potential (8). Although we could not detect the nests in our case, in order to identify the difference between basaloid cell nests beneath palmar pits and BCC, immunohistochemistry using BerEP4 (DAKO, Glostrup), anti-Ki67 antibody (DAKO) and anti-Gli1 antibody (SantaCruz, CA) was performed. Palmar pits from case 1 and sporadic case carrying a germ line mutation of *PTCH1*, 1408_1409insGGCT (5), odontogenic cyst from case 4 were analyzed. Interestingly, reactivity to BerEP4 was

strongly positive only in basaloid cell nests of sporadic case but not in the epidermis beneath the pits in both cases (figure D left). Gli1, which is transported into nucleus by activation of *Shh*-signal, was expressed in the nuclei of the basaloid cell nests of sporadic case, basal cell and suprabasal layer of epidermis beneath case 1's palmar pits and the cyst wall of case 4's odontogenic keratocyst (figure D and not shown). Ki67 was minimally expressed in these samples (data not shown). *Shh* signal is a well-known developmental factor highly expressed in fetus, and associated with Drosophila wing formation and vertebrate finger formation (9). In addition, previous report showed that the allelic loss of *PTCH1* gene could not be determined in the palmoplantar pits of NBCCS (10). These findings as well as our Gli1 immunostaining in indicate that palmoplantar pits require not only germ line *PTCH1* mutation but additional Gli1 activating factors, such as *shh*. Little malignant potential of the palmoplantar lesions might reflect the dependency on the physiological expression of *shh*.

Although Palmoplantar pits of NBCCS are sometimes indistinguishable from BCC even using well-known markers, unlike true BCC, the pathogenesis might be based on the partial loss of PTCH1 function and the physiological and location-specific *shh* expression during the development.

Conflict of Interest Statement

None declared

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FIGURE LEGENDS

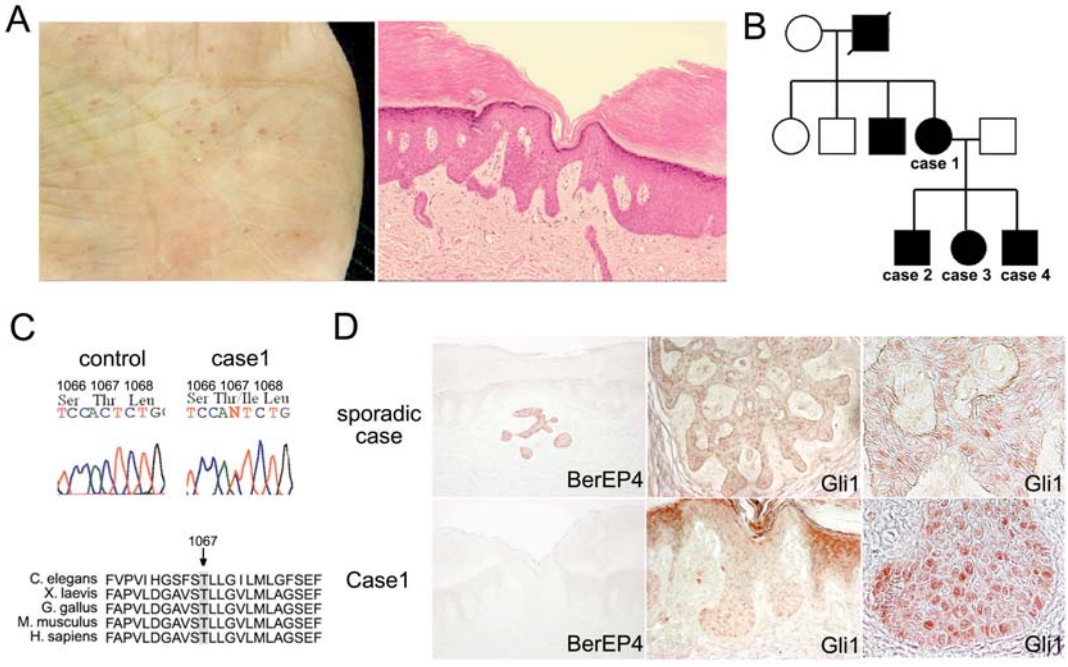
Figure

A. Palmar pits of Case 1 (left). Histopathology of the palmar pit (right). Basaloid cell nests could not be observed in multiple sections.

B. A pedigree of the patients

C. Result of direct sequencing of *PTCH1* gene. A missense-mutation, C3200T was identified in all affected family members. Comparison of the amino-acid sequence in the portion between several species is shown in lower panel.

D. Immunohistochemistry labeled with BerEP4 (left) and anti-Gli1 antibody (middle). Right panels show higher magnification of middle panels. Upper and lower panels show sections of same biopsied tissue from sporadic case and case 1, respectively.


A
B
case 1
case 2
case 3
case 4
C
control
case1
1066 1067 1068
Ser Thr Leu
TCCACTCTG
1066 1067 1068
Ser Thr/Ile Leu
TCCANTCTG
1067
C. elegans FVPVI HGSFSTLLG I LMLGFSEF
X. laevis FAPVLDGAVSTLLGVLMLAGSEF
G. gallus FAPVLDGAVSTLLGVLMLAGSEF
M. musculus FAPVLDGAVSTLLGVLMLAGSEF
H. sapiens FAPVLDGAVSTLLGVLMLAGSEF
D
sporadic case
Case1
BerEP4
Gli1
Gli1
BerEP4
Gli1
Gli1