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CASE LETTERS ▼

Novel mutation in PTCH1 gene in a patient with basal cell nevus syndrome and uterus bicornis*

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Dear Editor,

A 31-year-old white female was evaluated due to a history of multiple basal cell carcinomas (BCCs) since childhood. Examination revealed multiple papules and erythematous nodules on the face, back, and thorax, palmar pits, hypertelorism, frontal bossing, and increased volume in the left maxillary region (Figure 1). Basal cell nevus syndrome (BCNS) was diagnosed and a search was performed for involvement of other organs. Radiography of the jaw

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revealed an odontogenic keratocyst, confirmed by histology; computed tomography revealed calcifications of the falx cerebri and cerebellar tentorium; pelvic ultrasound diagnosed uterus bicornis. The patient's parents had no clinical signs of BCNS and are not consanguineous. Genetic testing directed at BCNS was performed. A peripheral venous blood sample was collected for DNA amplification by polymerase chain reaction and sequencing of all coding exons and 20 base pairs from the non-coding regions of the PTCH1 gene. Microarray-based comparative genomic hybridization was performed to detect large deletions and duplications involving all exons of the PTCH1 gene. Two heterozygous variants in the PTCH1 gene were detected: c.3487G> A, which predicts the substitution of glycine (Gly) by serine (Ser) at codon 1163; and c.2778G> T, which predicts the substitution of tryptophan (Trp) by cysteine (Cys) at codon 926. No deletions or duplications were detected in the PTCH1 gene. The patient's mother tested negative for both variants, but the father tested heterozygous for the variant c.3487G> A. The variant c.3487G> A was inherited from the father, suggesting a benign mutation. Meanwhile, the variant c.2778G> T is a *de novo* mutation, and according to amino acid prediction programs (PolyPhen, SIFT, MutationTaster) this variant is probably pathogenic (Figure 2).¹ To our knowledge, this variant had not been described previously. The patient has been followed-up for 12 years. Surgical excision, imiquimod, and photodynamic therapy with methyl aminolevulinate were the treatments performed.

Basal cell nevus syndrome (BCNS) or Gorlin-Goltz syndrome is an autosomal dominant disease. It is characterized by multiple BCCs, benign odontogenic keratocysts in the jaw, palmoplantar pits, defects of the skeletal and central nervous system (spina bifida and bifid ribs, calcification of the falx cerebri, agenesis of the corpus callosum) and facial dysmorphisms. Aberrant activation of the Hedgehog signaling pathway is associated with sporadic and hereditary BCC (BCNS) as well as other developmental defects.² The Hedgehog pathway plays an important role in embryonic development. Its aberrant activation is involved in the development of many malignancies, including virtually all BCCs, whether sporadic or involved in the BCNS.² Sonic Hedgehog binds to PTCH-



FIGURE 1: Multiple erythematous papules and hypertrophic scars on the trunk

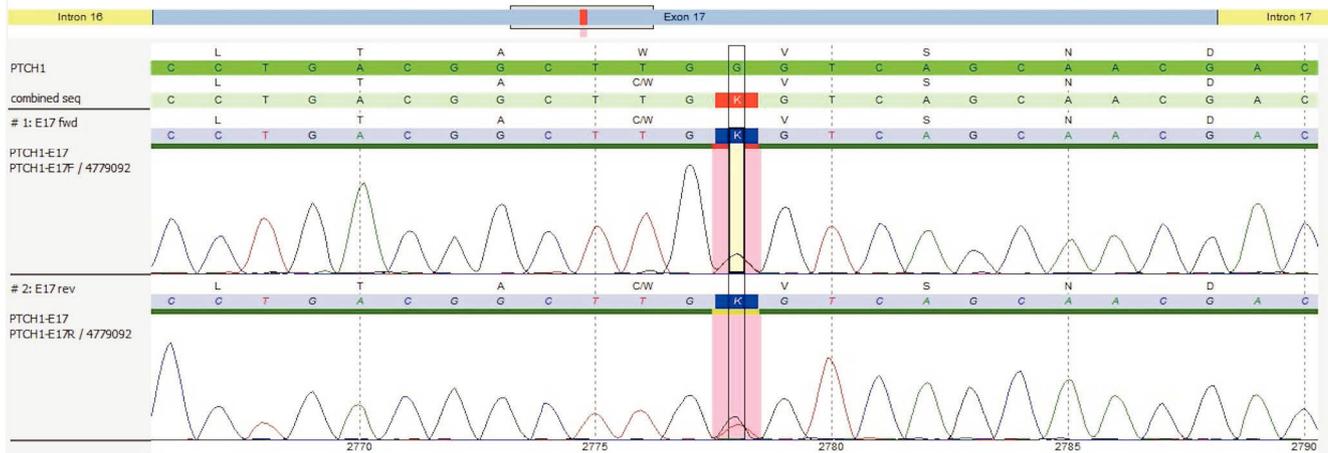


FIGURE 2: c.2778G>T variant, a de novo which changes Trp to Cys in codon 926

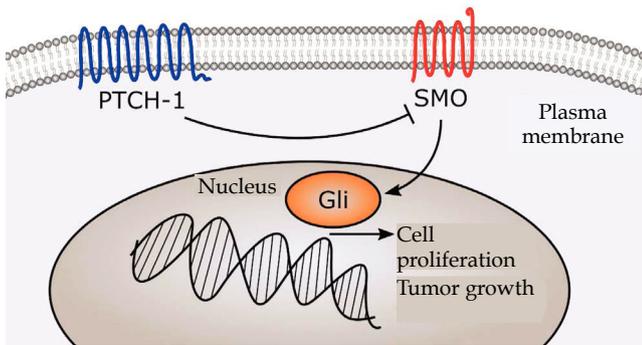


FIGURE 3: Sonic Hedgehog pathway

1, a tumor suppressor transmembrane protein. Thus, inhibition of smoothed (SMO) protein by PTCH-1 is undone. Activated SMO stimulates the transcription factor Gli, promoting cell proliferation and tumor growth (Figure 3). Aberrant activation occurs by loss of function in the PTCH-1 gene on chromosome 9q22.3-31 in 90%, and by activating mutations in the SMO gene in 10% of the BCCs.³

Substitution of Gly by Ser in codon 1163 of the PTCH1 gene has been described in healthy individuals and is considered neutral. The substitution of Trp by Cys at codon 926 of the PTCH1 protein is considered unfavorable.¹ This mutation has never been described in BCNS and may alter the function and structure of the encoded protein. These hypotheses are confirmed by the variant c.3487G> A in the PTCH1 gene in the father, suggesting that this change is benign; and by the c.2778G> T variant only in the patient, suggesting a *de novo* pathogenic mutation.

In the case reported here, the patient presented classic clinical characteristics of BCNS (multiple BCCs, odontogenic keratocyst in the jaw, palmar pits, hypertelorism, frontal bossing, calcification of the falx cerebri and cerebellar tentorium) and rare association with uterus bicornis, an incomplete fusion alteration of the Müller

ducts. This fusion process occurs during the first trimester of pregnancy, and most defects are sporadic, with few descriptions of genetic inheritance patterns.⁴ This is the second case of uterus bicornis in a patient with BCNS reported in the literature.⁵

We describe the c.2778G> T variant that leads to the substitution of Trp by Cys in codon 926 of the PTCH1 gene, a new pathogenic mutation that caused BCNS in a female patient with classic clinical findings of the syndrome, together with a rare association with uterus bicornis. Several developmental defects have been described from the aberrant activation of the Hedgehog pathway, and description of new genetic mutations and different clinical findings contribute to a better understanding of the disease, but further studies are required to confirm the hypothesis of Müllerian fusion defects associated with mutations in this pathway.□

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PHACE syndrome and hearing loss*

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Dear Editor,

PHACE syndrome (OMIM: 606519) is a neurocutaneous syndrome whose cardinal sign is the presence of infantile hemangioma located on the face, neck, or scalp accompanied by at least one of the following extracutaneous manifestations included in its

acronym: posterior fossa malformations, hemangiomas, arterial lesions, cardiac abnormalities/coarctation of the aorta, eye anomalies.¹ Patients with PHACE syndrome commonly seek medical care for treatment of the facial angiomatous lesions and the respiratory symptoms arising from subglottic or mediastinal angiomatous lesions.² However, recent case reports suggest a potential link between PHACE syndrome and hearing loss.³ A four-year old female patient with a diagnosis of PHACE syndrome presented with ipsilateral hearing loss and decreased visual acuity. There was a malformation in the posterior fossa, but without cognitive deficits or other abnormalities. The patient received multidisciplinary follow-up. Physical examination revealed cranial asymmetry. The angiomas were characterized as segmental hemangioma of infancy interspersed with apparently normal skin. The lesions extended across the left hemiface, upper lip, left cervical region, left shoulder, and upper left thorax (Figure 1). Orosopic examination showed an angiomatous lesion on the palate (Figure 2). Otosopic examination on the left revealed a narrowed external auditory canal, and the tympanic membrane (TM)



FIGURE 1: Appearance and location of lesions before treatment



FIGURE 2: Oroscopy showing soft palate involvement with infantile hemangioma

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