AUTHORS' CONTRIBUTIONS

Fabiane Mulinari Brenner ORCID 0000-0001-7970-522X
Approval of the final version of the manuscript; Conception and planning of the study; Elaboration and writing of the manuscript; Obtaining, analyzing and interpreting the data; Effective participation in research orientation; Intellectual participation in propaedeutic and/or therapeutic conduct of the cases studied; Critical review of the literature; Critical review of the manuscript.

Carolina Oldoni ORCID 0000-0003-1649-3076
Elaboration and writing of the manuscript; Obtaining, analyzing and interpreting the data; Critical review of the literature.

How to cite this article: *Brenner FM, Oldoni C. Telogen effluvium x female pattern hair loss: is there correlation? An Bras Dermatol. 2019;94(4):*486-7.

CASE LETTERS

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

Denis Miyashiro[1]
Luis Antonio Torezan[1]
Beni Moreinas Grinblat[1]
Cyro Festa Neto[1]

DOI: http://dx.doi.org/10.1590/abd1806-4841.20197449

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 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-

Received 10 July 2017.
Accepted 13 August 2018.
* Study conducted at the Department of Dermatology, Faculdade de Medicina, Universidade de São Paulo, São Paulo, SP, Brazil.
Financial support: None.
Conflict of interest: None.

[1] Department of Dermatology, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo, SP, Brazil.

Mailing Address:
Denis Ricardo Miyashiro
E-mail: denisrmiyashiro@gmail.com

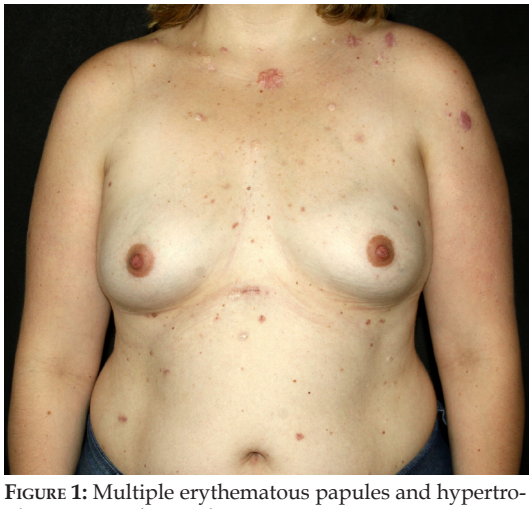

Figure 1: Multiple erythematous papules and hypertrophic scars on the trunk

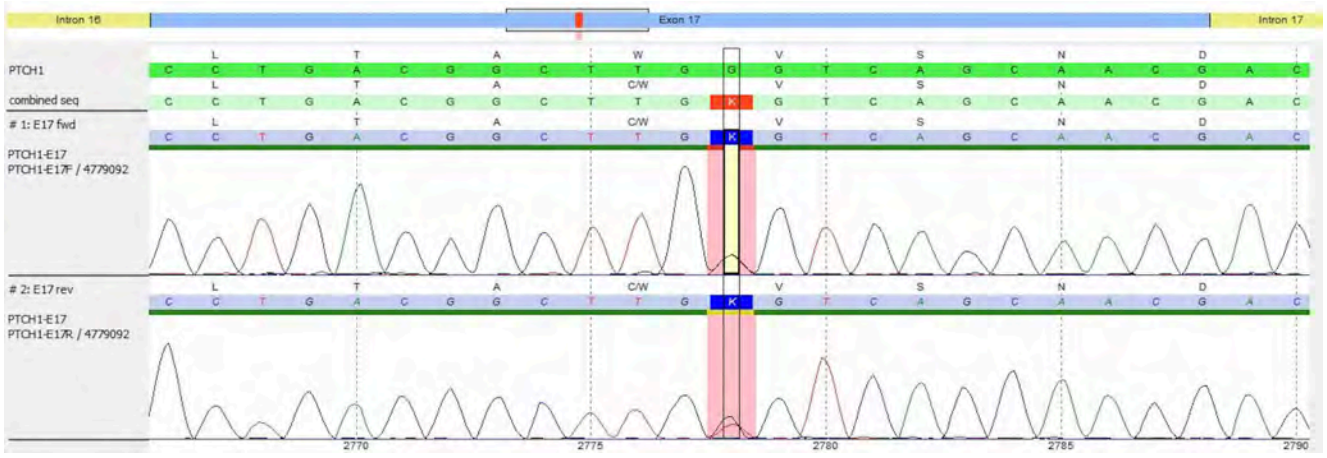

Figure 2: c.2778G>T variant, a de novo which changes Trp to Cys in codon 926

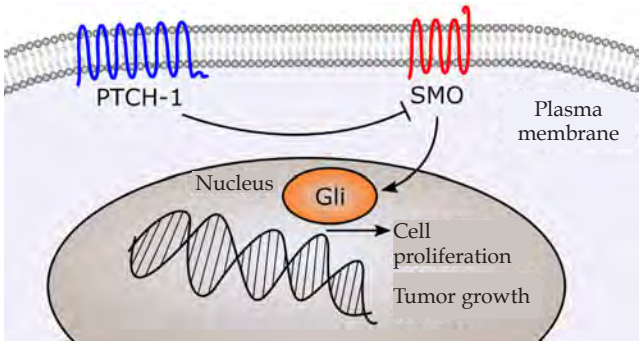

Figure 3: Sonic Hedgehog pathway

1, a tumor suppressor transmembrane protein. Thus, inhibition of smoothened (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.❑

REFERENCES

1. Schwarz JM, Rödelsperger C, Schuelke M, Seelow D. MutationTaster evaluates disease-causing potential of sequence alterations. Nat Methods. 2010;7:575-6.
2. Athar M, Li C, Kim AL, Spiegelman VS, Bickers DR. Sonic hedgehog signaling in Basal cell nevus syndrome. Cancer Res. 2014;74:4967-75.
3. Epstein EH. Basal cell carcinomas: attack of the hedgehog. Nat Rev Cancer. 2008;8:743-54.
4. Troiano RN, McCarthy SM. Mullerian duct anomalies: imaging and clinical issues. Radiology. 2004;233:19-34.
5. Ramaglia L, Morgese F, Pighetti M, Saviano R. Odontogenic keratocyst and uterus bicornis in nevoid basal cell carcinoma syndrome: case report and literature review. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2006;102:217-9.

AUTHORS' CONTRIBUTIONS

Denis Miyashiro ORCID 0000-0002-1959-4908
Approval of the final version of the manuscript; Conception and planning of the study; Elaboration and writing of the manuscript; Obtaining, analyzing and interpreting the data; Effective participation in research orientation; Intellectual participation in propaedeutic and/or therapeutic conduct of cases studied; Critical review of the literature; Critical review of the manuscript.

Luis Antonio Torezan ORCID 0000-0003-0482-6515
Approval of the final version of the manuscript; Conception and planning of the study; Effective participation in research orientation; Intellectual participation in propaedeutic and/or therapeutic conduct of cases studied; Critical review of the manuscript.

Beni Moreinas Grinblat ORCID 0000-0002-8571-5691
Approval of the final version of the manuscript; Effective participation in research orientation; Intellectual participation in propaedeutic and/or therapeutic conduct of cases studied; Critical review of the manuscript.

Cyro Festa Neto ORCID 0000-0003-3879-9981
Approval of the final version of the manuscript; Effective participation in research orientation; Intellectual participation in propaedeutic and/or therapeutic conduct of cases studied; Critical review of the manuscript.

How to cite this article: *Miyashiro D, Torezan LA, Grinblat BM, Festa Neto C. Novel mutation in PTCH1 gene in a patient with basal cell nevus syndrome and uterus bicornis. An Bras Dermatol. 2019;94*(4):487-9.

PHACE syndrome and hearing loss*

José Fernando Polanski[1,2]
Rodrigo de Oliveira Veras[2]
Lucas Resende Lucinda[1]
Vanessa Mazanek Santos[1]

DOI: http://dx.doi.org/10.1590/abd1806-4841.20197729

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 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). Oroscopic examination showed an angiomatous lesion on the palate (Figure 2). Otoscopic examination on the left revealed a narrowed external auditory canal, and the tympanic membrane (TM)

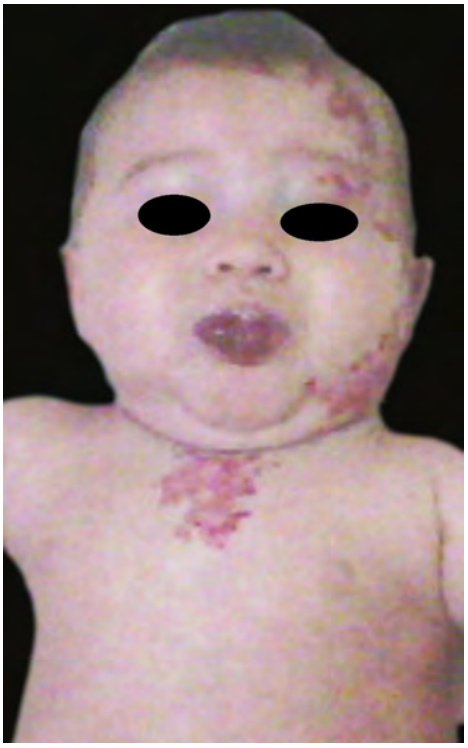

Figure 1: Appearance and location of lesions before treatment

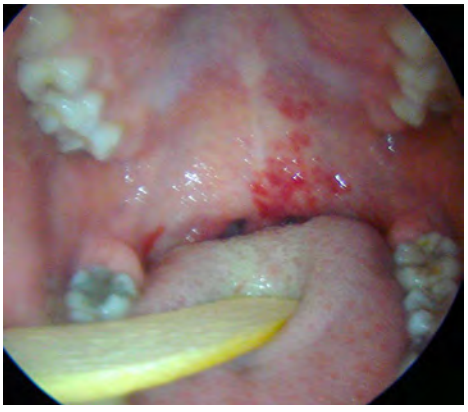

Figure 2: Oroscopy showing soft palate involvement with infantile hemangioma

Received 08 October 2017.
Accepted 12 August 2018.
* Study conducted at Hospital de Clínicas, Universidade Federal do Paraná, Curitiba, PR, Brazil.
Financial support: None.
Conflict of interest: None.

[1] Department of Otorhinolaryngology, Hospital de Clínicas, Universidade Federal do Paraná, Curitiba, PR, Brazil.
[2] Medical Student, Faculdade Evangélica do Paraná, Curitiba, PR, Brazil.

Mailing Address:
José Fernando Polanski
E-mail: jfpolanski@gmail.com