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PHOTOQUIZ

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Alopecia and hearing loss in a boy

Ngo Binh Trinh MD[1] | Hoang Anh Vu MD, PhD[2] | Anh Khoa Pham MD[3] | Waleed Adawi MS[4] | Stephanie A. Castillo MD[3] | Linh Ngoc Tuong Tran MD[5]

[1]Department of Venereology, Ho Chi Minh City Hospital of Dermato-Venereology, Ho Chi Minh City, Vietnam

[2]Center for Molecular Biomedicine, University of Medicine and Pharmacy at Ho Chi Minh City, Ho Chi Minh City, Vietnam

[3]Department of Dermatology, Eastern Virginia Medical School, Norfolk, VA, USA

[4]School of Medicine, Eastern Virginia Medical School, Norfolk, VA, USA

[5]Department of Otolaryngology, Ho Chi Minh City University Medical Center, Ho Chi Minh City, Vietnam

Correspondence
Ngo Binh Trinh, MD, Department of Venereology, Ho Chi Minh City Hospital of Dermato-Venereology, Ho Chi Minh City, Vietnam.
Email: mdbinhtrinh@gmail.com

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CASE REPORT

A 6-year-old boy presented to dermatology for evaluation of hair loss. He was born at term after an uneventful pregnancy. By the age of one, he had developed hearing loss and hair shedding. Dermatological examination showed thin, brittle hair on the scalp without evidence of scarring alopecia (Figure 1). Eyebrows and eyelashes were normal. No abnormalities of skin, nails, and testicles were detected. Liver and kidney function tests and evaluation for aminoacidemia, aminoaciduria, and iron metabolism were unremarkable. Developmental assessment showed intellectual disability. He had previously undergone audiological testing, which revealed profound sensorineural hearing loss at the cochlear level. Cochlear hair cells were impaired, but the external/middle ear and retro-cochlear pathway were intact. He started an audiological follow-up program and had begun wearing hearing aids at the age of 4 years. Electron microscopy of the hairs was carried out (Figures 2 and 3).

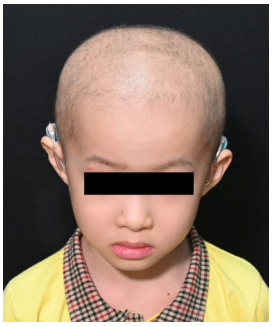

FIGURE 1

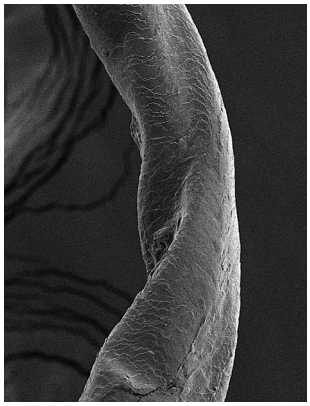

FIGURE 2

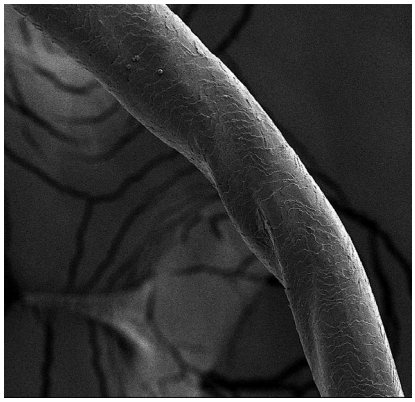

FIGURE 3

WHAT IS THE DIAGNOSIS?

Diagnosis: Bjornstad syndrome

Electron microscopy of hairs revealed flattening and twisting around the long axis. Molecular genetic analysis was conducted using the Sanger technique and detected two compound heterozygous variants in *BCS1L*. The first was a change of guanine to cytosine at nucleotide position 649 in exon 4, resulting in a substitution of aspartic acid by histidine at codon 217 (c.649G>C; p. Asp217His). The second was a change of guanine to adenine at nucleotide position 671 in exon 5, leading to a substitution of arginine by histidine at codon 224 (c.671G>A; p. Arg224His). Further investigation revealed that the patient's unaffected mother carried the heterozygous variant in exon 4 (c.649G>C; p. Asp217His), while his unaffected father had the heterozygous variant in exon 5 (c.671G>A; p. Arg224His). The hair and hearing examinations of his parents did not reveal any impairment.

DISCUSSION

Bjornstad syndrome is a rare inherited autosomal recessive disorder, characterized by pili torti and sensorineural deafness.[1] The hearing loss is of variable severity and often presents in the first year of life. Pili torti is a congenital or acquired hair abnormality in which the hair shaft is flattened and rotated at irregular intervals through approximately 180 degrees. As a result, hair in the eyebrow and eyelashes appears coarse, lusterless, and brittle; other body hair is not affected.[2] Given the symptoms of Bjornstad syndrome are limited, treatment beyond the use of hearing aids is not typically needed.

While hypotrichosis combined with hearing loss is a hallmark of Bjornstad syndrome, this combination can also be seen in oculodentodigital dysplasia, Woodhouse-Sakati syndrome, biotinidase deficiency, and Crandall's syndrome.[3] While pili torti and sensorineural hearing loss have been described in both Bjornstad syndrome and Crandall's syndrome, the latter is differentiated by hypogonadism.[1]

Approximately 15 different mutations in *BCS1L* have been reported in Bjornstad syndrome.[4-9] *BCS1L* encodes a chaperone protein within the ATPases associated with different cellular activities (AAA) family of ATPases. It is responsible for assembly of the mitochondrial complex III and the respirasome.[10] The *BCS1L* protein contains two functional domains, a BCS protein sorting domain (residues 1 through 89) and the AAA ATPase core (residues 200 through 399).[5] Mutations in the gene can lead to various phenotypes, ranging from lethal conditions such as GRACILE syndrome and complex III deficiency, to milder disorders such as Bjornstad syndrome. The phenotypic disease variants are associated with mutations in different regions of the *BCS1L* gene, with Bjornstad syndrome often having mutations isolated in the AAA domain. Of the 15 reported mutations reported in Bjornstad syndrome, only one is associated with the more severe, CIII deficiency.[4] Further research is needed to investigate the relationship between genotype and phenotype.

Here, we report a case of a novel compound heterozygous mutation in *BCS1L* in a patient with Bjornstad syndrome. Of the two variants detected, the c.671G>A (p. Arg224His) was reported with very low frequency in general population (A = 0.000012/3 according to GnomAD_exomes database). This variant has a polyphen-2 score of 1.0, suggesting pathogenic ability. The second variant, the c.649G>C (p. Asp217His), has not been reported before and has a polyphen-2 score of 0.296. Both mutations are in close proximity to the AAA domain, and we hypothesize the change to a larger amino acid will affect ATPase binding and function. Additional investigation is needed to elucidate the specific role these mutations play in the function of *BCS1L*.

ORCID

Ngo Binh Trinh https://orcid.org/0000-0002-3829-3115
Hoang Anh Vu https://orcid.org/0000-0003-4232-6001
Anh Khoa Pham https://orcid.org/0000-0002-9334-9054
Waleed Adawi https://orcid.org/0000-0003-1242-7960
Stephanie A. Castillo https://orcid.org/0000-0002-5353-2321
Linh Ngoc Tuong Tran https://orcid.org/0000-0002-7209-4849

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