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Trichothiodystrophy type 3 with a mutation in the *GTF2H5* gene: A case report in Argentina

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ABSTRACT

Trichothiodystrophy is a rare neuroectodermal defect characterized by sparse and brittle hair, photosensitivity, intellectual disability, and short stature. With an incidence of 1.2 per million in Western countries, half of the reported cases have clinical and cellular photosensitivity associated with mutations in three subunits of the general transcription factor IIH complex, which is involved in transcription and nucleotide excision repair.

Six patients *with GTF2H5* mutations have been reported; this is the first report in Argentina. The patient was diagnosed at 3 years of age by "tiger tail banding" on polarized light microscopy, and at 9 years of age, it was confirmed by molecular biology. She presented growth retardation with more severe stunting and underweight than reported.

Given the low prevalence and high clinical heterogeneity, a high index of suspicion is required for early diagnosis, interdisciplinary management, and genetic counseling.

Keywords: *trichothiodystrophy syndromes;* GTF2H5 *gene; photosensitivity disorders; ichthyosis; growth disorders.*

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INTRODUCTION

Tricotiodistrophy (TTD) is a genodermatosis with significant clinical variability, characterized by brittle hair with sulfur deficiency and typical "tiger tail" bands under polarized light microscopy, ichthyosis, photosensitivity, intellectual disability, and short stature. In most cases, its inheritance is autosomal recessive, with an overall incidence of 1.2 per million in Western countries.[1] Some are associated with mutations in the general transcription factor IIH (TFIIH) complex, which transcribes and repairs by nucleotide excision (NER) a wide range of DNA lesions, particularly those induced by ultraviolet light.[2] Bi-allelic loss-of-function mutations in *GTF2H5* have been associated with photosensitive trichothiodystrophy (PTTD) type 3 (OMIM 616395).[3]

We describe the clinical and genetic aspects of a patient with a *GTF2H5* gene mutation referred to the Growth and Development Service of the H. J. Notti Pediatric Hospital, Mendoza, Argentina. Informed consent was obtained and approved by the institution's Ethics and Research Committee (act 97/2024).

CLINICAL CASE

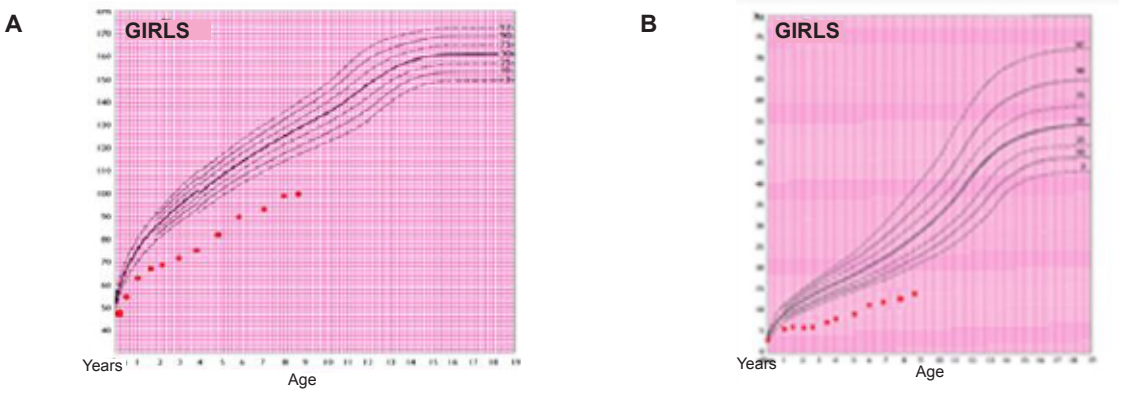
We present a nine-year-old girl, the sixth child of a non-consanguineous couple. Her parents are of Bolivian origin, and she was born at full term with adequate size and no relevant family history. When she was 12 months old, she was referred to the Growth and Development Service because of postnatal growth retardation with low weight, severe short stature and microcephaly (*Figure 1*). She was underweight with a Z-score (Z) of -3.48, severe short stature (Z -4.52), normal weight for height, microcephaly (Z -3.6), and developmental delay. She presented with short, coarse, sparse, curly, and brittle hair; sparse, short, and thin eyebrows and eyelashes; seborrheic eczema of the neck and scalp; skin with fine desquamation and erythematous base; and signs of photosensitivity. In addition, brachydactyly, onychodystrophy, and misaligned teeth with a yellowish tint and polycaries were evidenced (*Figure 2*).

By way of background, she was hospitalized at the age of 2 months for urosepsis by *E. coli*, impetiginized dermatitis, and acute malnutrition.

During her follow-up, the laboratory test results were normal, which included hemacytometry, renal, hepatic, and thyroid function; immunochemistry for celiac disease; phosphorus, calcium and iron metabolism; hemoglobin electrophoresis; growth hormone determination under the stimulus, immunological profile, sweat test, determination of vitamins D and B12, zinc and copper, organic acids, acylcarnitines, mycological nail culture. Abdominal ultrasound, skeletal radiographs, and brain MRI were normal with delayed bone age. The ophthalmological evaluation was normal, and the neurological evaluation showed only neurodevelopmental compromise and microcephaly, with no other alterations during the physical examination.

The trichothiodystrophic syndrome was suspected at 3 years, and a trichological examination was requested with electron microscopy, revealing a brindle appearance with a change in polarization compatible with

Figure 1. Anthropometric data of the patient along the follow-up in the reference curves of Argentine girls

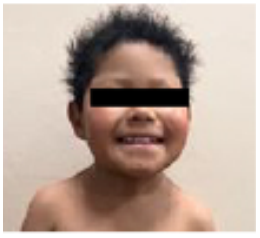


A. Stature for age. B. Weight for age.

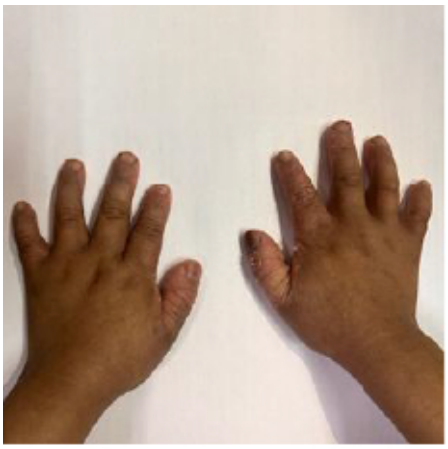
Source: Charts prepared by Lejarraga H and Orfila J. Arch Argent Pediatr. 1987;85:209-222.

Figure 2. Clinical characteristics of the patient

A



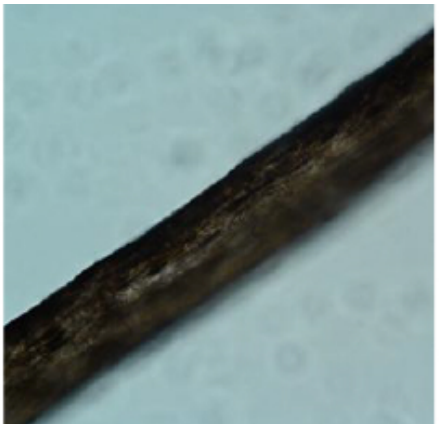
B



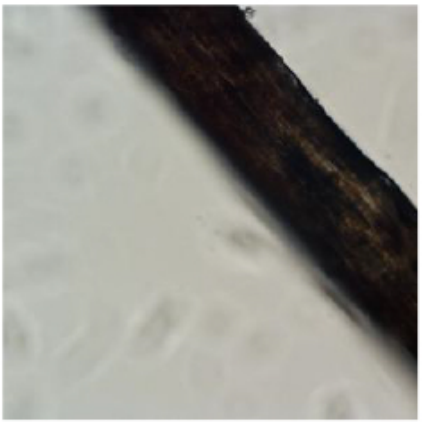
A. Dry skin with ichthyosis and photosensitivity, and sparse, brittle hair.
B. Brachydactyly, onychodystrophy, scaly skin with erythematous base, and signs of photosensitivity.

Figure 3. Trichological examination

A



B



A. The hair appeared brittle, ribbed at low magnification; at higher magnification with direct light, showed characteristic light and dark regions called "tiger tail".
B. Changes to polarization with polarized light.

TTD (*Figure 3*). Recently, at 9 years of age, due to the new availability of molecular studies, exome sequencing was performed by next-generation sequencing detecting the variant c.2T>C (p.Met1Thr) in homozygosis in the *GTF2H5* gene (ClinVar ID 2136487), classified as probably pathogenic according to the criteria of the American College of Medical Genetics (PVS1, PM2, PP5). Due to the clinical picture and trichological study, compatible with the molecular finding, a variant of probably a pathogenic category in the *GTF2H5* gene in the expected zygosity for a pathology with autosomal recessive inheritance, such as the one presented, the corresponding genetic counseling was performed on the family. None of her relatives presented clinical manifestations. Confirmation of the Sanger variant could not yet be performed on the girl or the parents because the technique is unavailable in our hospital. The parents are elderly (her mother is 47 years old, and her father is 51 years old), and the mother has tubal trypsia. The siblings were advised to perform a carrier search and complete genetic counseling.

DISCUSSION

TTD is a rare neuroectodermal defect with high clinical heterogeneity, being the common characteristic of fragile and sparse hair, skin, growth, and neurodevelopmental alterations.[1,4,5]

As for its molecular etiology, it also presents high gene heterogeneity and variable expressivity. Two distinct forms of TTD have been identified according to the presence or absence of clinical and cellular photosensitivity, both with a different genetic basis.[6]

Approximately half of the reported TTD patients belong to the photosensitive group associated with pathogenic variants associated with biallelic mutations in three genes: *ERCC3*, *ERCC2*, and *GTF2H5*, encoding different subunits of TFIIH.4 Depending on the affected gene, these are classified as TTD1, TTD2, and TTD3, respectively.[7] TFIIH is essential for both transcription initiation and DNA NER. The NER affected by these mutations easily explains the photosensitive phenotype, as this repair process is the only pathway in human cells capable of eliminating solar ultraviolet-induced injury.[8]

The remaining half of patients with TTD with competent NER are categorized as non-photosensitive TTD; these also show a wide genetic and clinical heterogeneity, mainly without presenting skin lesions secondary to low UV exposure.[9]

Six patients with *GTF2H5* mutations have

Table 1. Genotypic-phenotypic characteristics of patients with TTD3 reported to date

Patients TTD3	*GTF2H5* Mutation	Skin and appendages	Neuro-development	Growth	Phenotype Infections	CNS	Cardiovascular	Dysmorphia	Other
2004,Giglia-Mari TTD1BR	c.166C>T (p.Arg56Ter) c.62T>C (p.Leu21Pro) heterozygous compound	Congenital ichthyosis Collodion baby Photosensitivity Eczema Brittle hair	MR	Sort stature	NR	NR	NR	Cataracts	
2004,Giglia-Mari TTD99RO	c.166C>T (p.Arg56Ter) homozygous	Congenital ichthyosis Photosensitivity Brittle hair	MR	short stature	NR	NR	NR		
2004,Giglia-Mari TTD13/14PV	c.2T>C (p.Met1Thr) homozygous	Photosensitivity Brittle hair	MR	Short stature	NR	NR	NR	Deafness	
2014, Moriwaki	c.166G>C (p.Glu55Ter) homozygous	Congenital ichthyosis Collodion baby Photosensitivity Brittle hair	MR	Normal	No	No	No	Cataracts	
2019, Michalska	c.49A>T (p.Lys17Ter) c.29T>A (p.Ile10Lys) heterozygous compound	Congenital ichthyosis Collodion baby Alopecia Onychodystrophy	Not assessable	IUGR SGA Post-natal growth retardation	Congenital pneumonia HAIs	Delayed myelination, Dilatation of ventricles Structural alteration of frontal lobes Trigonocephaly	NR	Microphtalmia Hypertelorism Ectropiodn Eclabium Neonatal teeth Neonatal teeth	Prematurity Piloric estenosis Meckel diverticula Bilateral cryptorchidism
2023, Sorrentino	c.148_160delGTTAATGTCCTC CinsTAATAGCTCCTGG p.(Val50Ter) homozygous	Congenital ichthyosis Collodion baby Brittle hair Alopecia	Neonatal hypotonia	IUGR SGA	Multiple	Vermix, hypoplasia Cerebellar dysplasia Dilatation of the fourth ventricle and lateral ventricles	VSD ASD Overriding aorta Carotid artery malformation	Hearing disorders	Prematurity Bilateral cryptorchidism Acute renal failure Nephrocalcinosis
Proband	c.2T>C homozygous (p.Met1Thr)	Photosensitivity Brittle hair Eczema Onychodystrophy Ichthyosis	MR	Short stature Post-natal growth retardation	Urosepsis	Microcephaly	No	Yellowish teeth Caries Brachydactily	

ASD: atrial septal defect; VSD: ventricular septal defect; HAIs: health care associated infections; NR: not reported; SGA: small for gestational age; IUGR: intrauterine growth restriction; MR: mental retardation; CNS: central nervous system; TTD: trichothiodystrophy.

Table modified from Sorrentino U, Agosto C, Benini F, Bertolin C, Cassina M, Bonadies L, et al. Severe trichothiodystrophy and cardiac malformation in a newborn carrying a novel GTF2H5 *homozygous truncating variant. Clin Genet. 2023;104(5):604-6.*

been reported worldwide; to our knowledge, this is the first report in Argentina (*Table 1*).

The diagnostic criteria for TTD are based on the presence of at least two of four clinical or laboratory abnormalities: (1) brittle hair and/or hair shaft abnormalities; (2) tiger tail bands with polarized microscopy; (3) decreased sulfur or cystine content of the hair; and (4) abnormality in DNA repair. The age range at diagnosis of TTD is between 3 months and 47 years, with an average of 6 years.[4]

In our patient, TTD was diagnosed at age 3 for hair alterations and "tiger tail" bands in polarized light microscopy. PTTD was confirmed at the age of 9 by molecular biology, with a *GTF2H5* gene mutation in homozygosis.

Brittle hair and photosensitivity are common features of all PTTDs;[5] the onset of photosensitivity is described between the ages of 3 and 7.[1,5] The girl we present in this case had photosensitivity since she was 2 months old.

Congenital ichthyosis and collodion membrane described in 65% and 9%, respectively, of patients with TTD are other manifestations present in most patients with bi-allelic mutations in *GTF2H5* at birth but not found in this patient.[1,3]

The patient described presented onychodystrophy, similar to that reported,[2,4] neurological involvement, microcephaly, and developmental delay, as most patients with *GTF2H5* mutation.

The patient presented postnatal growth retardation, with low weight (Z -3.48) and short stature (Z -4.52) more severe than published. Overall, patients with TTD have considerable growth abnormalities, with a mean Z height-for-age of -2.75 and PZ weight-for-age of -2.60, with adequate weight-for-height and normal nutritional laboratory parameters.[4,10,11] In previously reported patients with *GTF2H5* mutation, most had short stature; two had prenatal growth restriction and one had normal growth.

Susceptibility to infections has been described; this patient presented sepsis with urinary focus, and immunodeficiencies were ruled out.[1-3]

The girl reported here presented yellowish teeth with caries; sparse, short, thin eyebrows and eyelashes; and craniofacial dysmorphia, as described by Pascolini et al. in patients with PTTD. Ocular and auditory alterations have been described but were not found in this patient.[1-4,7,12]

This is the first case of PTTD type 3 with *GTF2H5* mutation reported in Argentina and the seventh case worldwide. Being a rare disease with multisystemic involvement and high clinical heterogeneity, it requires a high index of suspicion for early diagnosis, interdisciplinary management, and appropriate genetic counseling. ■

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