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CLINICAL REPORT

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A novel *MPLKIP*-variant in three Finnish patients with non-photosensitive trichothiodystrophy type 4

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Abstract

Trichothiodystrophy is a group of multisystem neuroectodermal disorders with dysplastic hair as the cardinal symptom. We describe three patients from two Finnish families in whom whole-exome sequencing revealed a novel homozygous variant, c.26del, p.(Pro9Glnfs*144) in the *MPLKIP*-gene, confirming the diagnosis of non-photosensitive trichothiodystrophy type 4 (TTD4). The variant was confirmed by Sanger sequencing and inherited from unaffected carrier parents. This report adds to the literature by expanding the genetic and phenotypic spectra of *MPLKIP*-related trichothiodystrophy. We describe dysmorphic features in the patients and provide a comparison of clinical characteristics in patients with TTD4 reported to date.

KEYWORDS
C7orf11, tiger tail, trichorrhexis, trichoschisis, TTD4, *TTDN1*

1 | INTRODUCTION

Trichothiodystrophy (TTD) is an ultra-rare, autosomal recessive neurocutaneous disorder described in 1968 (Pollitt, 1968). The name TTD refers to a group of disorders characterized by sulfur-deficient, brittle hair, giving rise to a characteristic alternating light and dark appearance called "tiger tail banding" of the hair under polarizing microscopy (Liang, 2005). In addition to the dysplastic hair, the diagnostic hallmark of the disorder, patients with TTD may exhibit a variety of associated features, including intellectual disability, growth retardation, ataxia, seizures, ichthyosis, and hypogonadism (Table 1).

TTD is divided into photosensitive and non-photosensitive forms. About half of the patients have photosensitive TTD, a nucleotide excision repair (NER) disorder causing cellular and clinical hypersensitivity to UV light. These individuals have variants in transcription factor IIH (TFIIH) subunit genes. In the non-photosensitive form of TTD, however, patients lack cutaneous photosensitivity and are NER proficient. *MPLKIP* (M-phase-PLK1-interacting protein, MIM 60918, synonyms *TTDN1*, *C7orf11*) was the first causative gene identified as underlying non-photosensitive TTD and causes TTD4 (MIM 234050) (Nakabayashi, 2005). Recently, the genes *RNF113A*, *GTF2E2*, and *TARS1* were identified as causing other non-photosensitive TTD subgroups (TTD5-TTD7). For some patients, the molecular cause is unknown (Theil, 2019).

Here, we report clinical, molecular, histological, and imaging data on three Finnish patients from two families with non-photosensitive TTD4, caused by a novel homozygous variant in *MPLKIP*.

TABLE 1 Spectrum of *MLPKIP*-variants and associated clinical features in patients with non-photosensitive trichothiodystrophy

Reference	Ethnicity or origin of study	Number of patients (families)	Age (y) at last examination	*MPLKIP*-variant	Zygosity	Ataxia	Growth retardation or delayed bone age	Develop-mental delay	Micro-cephaly
Heller et al., 2015	Caucasian	1	14	c.2T>G, p.(Met1Arg)	CMPD	–	–	+	N/A
				c.2T>C, p.(Met1Thr)	HTZ				
Heller et al., 2015	Caucasian	1	4	c.227delG, p.(Gly76Alafs*77)	CMPD	–	+	+	N/A
				gross deletion ~120 kb	HTZ				
Heller et al., 2015	Caucasian	2 (1)	1-2	c.277delT, p.(Ser93Profs*60)	CMPD	–	+	+	N/A
				Gross deletion of ~92kb	HTZ				
Heller et al., 2015	Caucasian	1	24	c.278insTCTA and ~5 kb deletion starting at c.279 spanning exons 1-2	HMZ	–	+	+	N/A
Trujillano et al., 2017	Middle East	1	12	c.85G>T, p.(G29*)	HMZ	N/A	N/A	+	N/A
Nakabayashi et al., 2005; Przedborski et al., 1990	Morocco	3 (1)		c.187_188delGG, p.(Gly46Glyfs*13)	HMZ	+	+	+	+
Nakabayashi et al., 2005; Rizzo et al., 1992	Italian	1		Gross deletion of exon 2 and parts of exon 1	HMZ	N/A	–	+	–
Nakabayashi et al., 2005; Jackson et al., 1974; Baden et al., 1976	Amish	13 affected relatives genotyped		c.430A>G, p.(Met144Val)	HMZ	–	+	+	N/A
Botta et al., 2007			Age at dg						
	Italy	1	4	c.148_152delCACAC, p(His50Alafs*8)	HMZ				
	Italy	1	3	c.277delT, p.(Ser93Profs*60)	CMPD				
				c.148_152delCACAC, p(His50Alafs*8)	HET	Clinical features reported as a group for at least some of the cases reported by Botta et al., variant-specific features not available.			
	Italy	1	8	11-30 kb whole gene deletion	HMZ	Reduced coordination	+	+ (all)	+
	The Netherlands	1	3	c.277delT, p.(Ser93Profs*60)	HMZ				
	Kuwait (Indian)	1	3	~ 150kb whole gene deletion	HMZ				
	Indian	1	6	c.229delC, p.(Arg77Glyfs*76)	HMZ				

TABLE 1 (Continued)

Reference	Ethnicity or origin of study	Number of patients (families)	Age (y) at last examination	*MPLKIP*-variant	Zygosity	Ataxia	Growth retardation or delayed bone age	Develop-mental delay	Micro-cephaly
Shah et al., 2016	Pakistan	9 (3)	8-38	c.339+1G>A	HMZ	N/A	+	+	N/A
Pollitt et al., 1968	N/A	2 (1)	3-5	c.326delA, p.(Gln109Argfs*44)		Wide-stance	+	+	+
Swagemakers et al., 2014						gait			
Zhou et al., 2018	China	1	16	c.92dupC, p.(Gly33Argfs*27)	HMZ	N/A	+	+	N/A
Pode-Shakked et al., 2015	Arab-muslim descent	9 affected relatives genotyped	2-36	c.505dupA, p.(Thr169Asnfs*32)	HMZ	N/A	N/A	+	N/A
La Serna-Infantes et al., 2018	Peru	1	8	125kb deletion covering *MPLKIP* and *SUGCT*	HMZ	–	+	+	+
Kalayci et al., 2019[c]	Turkey	1	N/A	c.505dupA, p.(Thr169Asnfs*75)	N/A[c]	N/A	+	+	N/A
	Turkey	3 (1)	N/A	c.85G>T, p.(G29*)	N/A[c]	N/A	+	+	N/A
	Turkey	1	N/A	c.61delT, p.(Trp21Glyfs*132)	N/A[c]	N/A	+	+	N/A
Pande et al., 2020	India	2 (1)	13, 16	c.229del, p.(Arg77Glyfs*76)	HMZ	N/A	+	+	+
Current study	Finland	3 (2)	17-19	c.26del, p.(Pro9Glnfs*144)	HMZ	+	+	+	+

Reference	Dys-morphic hair	Nail dystrophy	Skin abnormality	Dysmorphic features	Gonadal dysfunction	Tiger tail pattern[a]	Hair shaft abnormality, other[b]	Cardiac abnormality	Recurrent infections	Other
Heller et al., 2015	+	+	Xerosis	+	N/A	+	+	–	+	Mildly photophobic, autism, osteopenia, unilateral left kidney, myopia, nystagmus, normal brain MRI
Heller et al., 2015	+	+	Xerosis	Some	N/A	+	+	Right-sided aortic arch left aberrant subclavian artery	–	Hyperopia, strabismus
Heller et al., 2015	+	+	Follicular papules	Some	N/A	+	+	ASD, Pulmonal stenosis	+	Seizures
Heller et al., 2015	+	+	Xerosis	Some	N/A	+	+	–	+	Epilepsy, severe skin photosensitivity, autism
Trujillano et al., 2017	N/A	N/A	Hyperkeratosis	+	N/A	N/A	N/A	N/A	N/A	Spasticity, hypoplasia of the frontal lobes

(Continues)

TABLE 1 (Continued)

Reference	Dysmorphic hair	Nail dystrophy	Skin abnormality	Dysmorphic features	Gonadal dysfunction	Tiger tail pattern[a]	Hair shaft abnormality, other[b]	Cardiac abnormality	Recurrent infections	Other
Nakabayashi et al., 2005; Przedborski et al., 1990	+	–	–	+	+	+	+	N/A	N/A	Osteopenia
Nakabayashi et al., 2005; Rizzo et al., 1992	+	+	Ichtyosiform areas	+	N/A	+	+	N/A	N/A	Hypotonia and severe nervous system impairment, unilateral optic atrophy, dental abnormalities, partial agenesis of corpus callosum, cortical atrophy, decreased cysteine content of hair
Nakabayashi et al., 2005; Jackson et al., 1974; Baden et al., 1976	+	+	–	N/A	Decreased fertility	+	+	N/A	N/A	Originally called Amish brittle hair syndrome (ABHS). Decreased sulfur content of hair.
Botta et al., 2007	+ (all cases)	+	ichthyosis	+	N/A	+	N/A	N/A	N/A	Decreased sulfur content of hair in some
Shah et al., 2016	+	+	–	+	N/A	+	+	Mitral regurgitation, all cases	+	Dental and ocular abnormalities epilepsy
Pollitt et al., 1968	+	+	Dry skin	N/A	N/A	N/A	+	N/A	N/A	Originally called Pollitt syndrome
Swagemakers et al., 2014										Poor quality teeth, low cysteine content of hair
Zhou et al., 2018	+	N/A	–	+	+	+	N/A	No	N/A	Bilateral cataracts
Pode-Shakked et al., 2015	Yes	N/A	Xerosis	m	+	+	+	Minimal mitral and tricuspidal regurgitation	N/A	Renal failure, pancytopenia, splenomegaly, dental abnormalities in one patient
La Serna-Infantes et al., 2018	+	+	Follicular keratosis	+	N/A	N/A	+	–	–	Dental caries and teeth decay
Kalayci et al., 2019[c]	N/A	N/A	Ichthyosis	+	Hypogonadism	+	N/A	N/A	N/A	
	N/A	N/A	Ichthyosis	+	Hypogonadism	+	N/A	N/A	N/A	
	N/A	N/A	Ichthyosis	+	Hypogonadism	+	N/A	N/A	N/A	
Pande et al., 2020	+	+	Ichthyosis	+	-	+	+	-	-	
Current study	+	+	+	+	+	+	+	Small ASD, PDA in one	–	Childhood epilepsy, stereotypic hand movements Growth hormone deficiency

Note: In case more than one patient harbors the same variant, a clinical feature is reported as being present (+) if manifested by at least one patient with that specific variant.

Abbreviations: +, present; –, absent; CMPD HTZ, compound heterozygous; HMZ, homozygous; N/A not available/assessed; Y, year old.

[a]Tiger tail appearance under polarizing light microscopy.

[b]Hair shaft abnormalities under light or scanning electron microscopy, including one of the following: Lack of scales, flattening of hair shaft, irregular and grooved surface, pili torti (twisted hair), trichoscisis (clean transverse fracture) and trichorrexis nodosa-like fractures.

[c]Only conference abstract available.

2 | SUBJECTS AND METHODS

The patients and families gave written informed consent for publication of clinical data and Family 1 for publication of unrecognizable photographs. Whole-exome sequencing (WES) (CentoXome Gold) was performed in a diagnostic laboratory (CENTOGENE, Germany). DNA from blood was used for WES and target regions enriched with the Twist Human Core Exome Plus kit. The library generated was sequenced on the Illumina platform HiSeq 4000 to obtain at least 20x coverage depth for >98% of the targeted bases. An in-house bioinformatics pipeline was applied. Disease-causing variants in HGMD®, ClinVar, and CentoMD® and variants with minor allele frequency (MAF) < 1% in the gnomAD database were considered, focusing on coding exons and flanking +/−20 intronic bases. Annotation of the *MPLKIP*-gene is according to NM_138701.3.

3 | RESULTS

All three patients harbored a rare homozygous variant in *MPLKIP*, c.26del, p.(Pro9Glnfs*144), creating a shift in the reading frame and a premature stop codon (hg19 chr7:40174141del9) 143 positions downstream. The variant is rare in the control population, which included no homozygotes: It is reported in 3 of 202,718 alleles (MAF 0.00001480) and present in the non-Finnish European subpopulation only (gnomAD v2.1.1). It was classified as pathogenic according to the American College of Medical Genetics and Genomics (ACMG) guidelines (Richards, 2015). The variants were confirmed by Sanger sequencing. Heterozygosity was confirmed in the parents. We have submitted the variant to a public database; the Leiden Open Variant Database (https://www.LOVD.nl).

4 | PATIENTS

The probands were three girls from two separate families, born to non-consanguineous Finnish parents (Figure 1). The families are not known to be related but reside in the same geographical region in Western Finland, suggesting a founder effect in this region that previously acted as a genetic isolate and where some autosomal recessive conditions are enriched (Varilo, 1996). The older sister from Family 1 (Proband II-3, Figure 1(a)) was born at term after an uneventful pregnancy with normal birth size (birthweight 3560 g, length 50 cm, head circumference 33 cm). She had global developmental delay and was later diagnosed with mild intellectual disability. She reached independent walking at age 26 months. She had ataxia with onset before the age of 2 years. As a child, she exhibited stereotypic hand movements. She also had epilepsy and later became seizure-free with a normal follow-up electroencephalogram (EEG). On one occasion in early childhood, she temporarily lost all hair on her scalp. She grew slowly, with delayed bone age and late puberty. Her head circumference (hc) was −3 standard deviations (SD). At age 18 years, she was 163.5 cm tall, corresponding to −0.6 SD (the mid-parental height was 0.8 SD).

At examination, epicanthus, long nose, short philtrum, full lips, high-arched palate, low hanging columella, hypoplastic alae nasi, long palpebral fissures (giving an impression of large eyes), sparse eyebrows, and low-set ears were noted. Her hair was dysplastic, with occasional patchy hair loss on the scalp. She had pes planovalgus, sandal gap, slender extremities and fingers, thoracic scoliosis, and kyphosis. The skin was dry with keratosis pilaris, the nails were slightly dysplastic, longitudinally ridged, and distally brittle. Brain magnetic resonance imaging (MRI) and computer tomography of the brain were normal. Dental examination was unremarkable. Ophthalmological examination showed restricted peripheral visual fields.

The younger sister from Family 1 (Proband II-4, Figure 1) was born at term after a normal pregnancy and with normal birth size (birthweight 3325 g, length 49.5 cm, hc 32 cm). In infancy, feeding difficulties and hypotonia were noted, and she had an episode of hair loss. Like her sister, she exhibited stereotypic hand movements in childhood. She had developmental delay and was later diagnosed with mild intellectual disability. She reached independent walking at age 18 months and produced words at age 2 years. She had ataxia with onset before the age of 2 years. She had no seizures. She had delayed bone age and growth retardation. At age 16.5 years her height was 149.3 cm (−2.9 SD), well below the mid-parental height (0.8 SD). Her hc was small, −3 SD. She received hormone treatment for delayed puberty due to hypergonadotropic hypogonadism.

At examination, she had short philtrum, low hanging columella, high-arched palate, hypoplastic alae nasi, and long palpebral fissures (giving an impression of large eyes). She also had thoracic kyphosis, dry palmar skin, pes planovalgus, and sandal gap. The nails were longitudinally ridged and brittle and the hair dysplastic. Brain MRI at age 2 years was normal except for somewhat delayed myelination. EEG was normal. An MRI scan of the abdomen visualized only one ovary. Ophthalmological evaluation showed small-angled squint (esotropia) and she was mildly photophobic.

The third patient (Proband II-1 from Family 2, Figure 1(a)) was born at term following a pregnancy complicated by gestational diabetes. Her birth size was normal (birthweight 3120 g, length 49.5 cm, hc 33.5 cm). She was hypotonic, had global developmental delay, and was subsequently diagnosed with moderate intellectual disability. She started walking at age 17 months and producing words at age 2.5 years. She had ataxia with onset before the age of 2 years. At age 20 months, her relative height was down to −4 SD and she was diagnosed with growth hormone (GH) deficiency for which she received GH treatment. At the age of 15 years, her height was 152.5 cm (−2.0 SD), below the mid-parental height of −0.6 SD. Her head size was below −1 SD during childhood, although within the normal range at age 16 years (54.5 cm). Her puberty was delayed, and she received hormone treatment for gonadal dysfunction.

At examination, epicanthus, hypertelorism, sparse eyebrows, low-set ears, long nose, long palpebral fissures (giving an impression of large eyes), fullness of upper eyelid, full lips, high-arched palate, short philtrum, low hanging columella, and hypoplastic alae nasi were noted. The hair was dysplastic, the nails dysplastic and dyschromic. She had slender extremities, short neck, thoracic kyphosis, dry palmar skin.

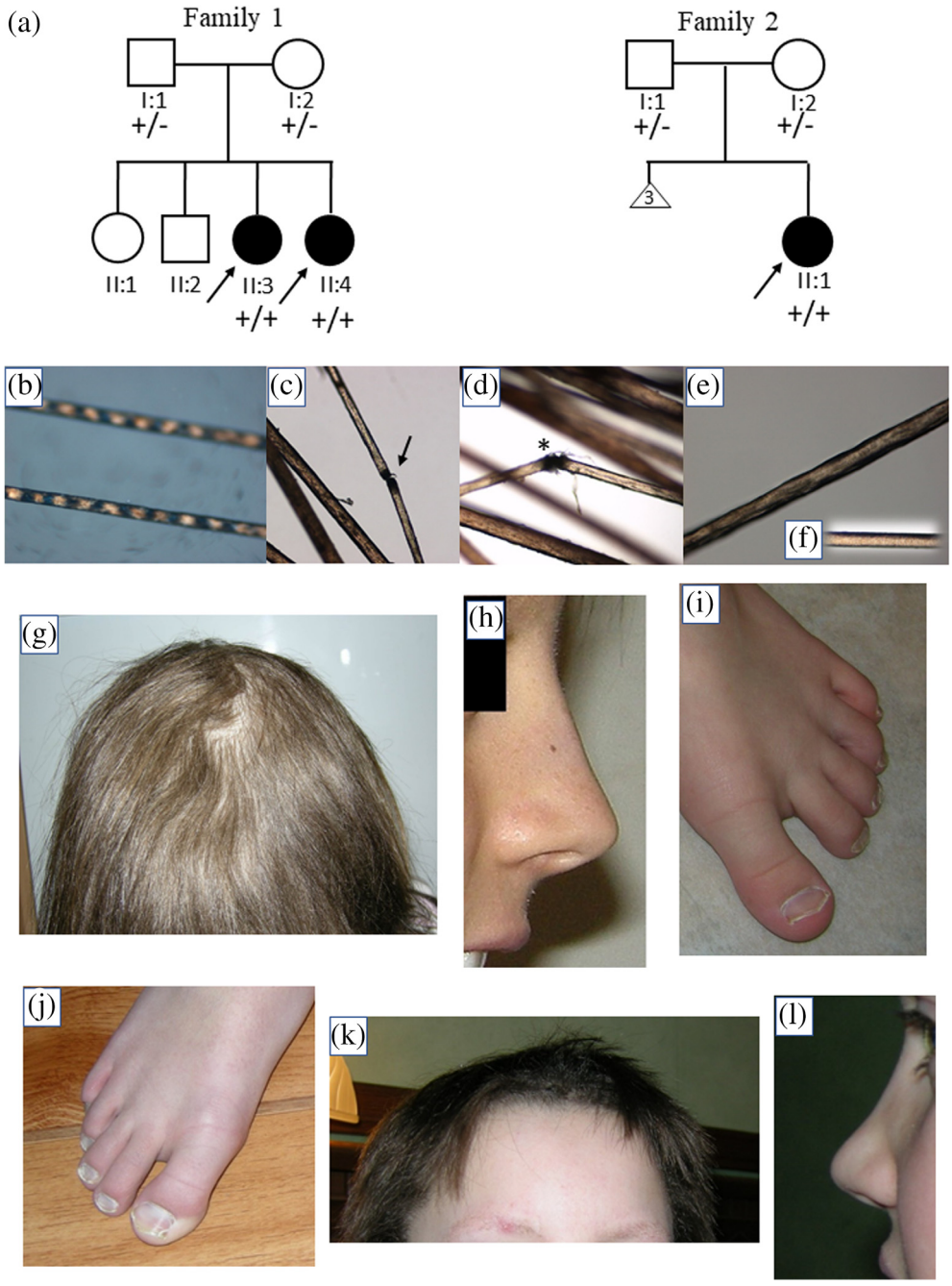

FIGURE 1 (a) Pedigrees of the families with non-photosensitive trichothiodystrophy type 4 co-segregating with a homozygous *MLPKIP*-variant c.26del, p.(Pro9Glnfs*144). Probands are designated with arrows and affected members indicated in black. Pluses and minuses under the symbols designate the molecular diagnosis (+/– and +/+ indicate heterozygous and homozygous states for the *MPLKIP* variant, respectively). (b) – (e) show hair shaft abnormalities typical of trichothiodystrophy and present in all three probands. (b) Tiger-tail banding under polarizing microscopy. (c) Trichoschisis (arrow), (d) trichorrhexis nodosa-like defect (asterisk), (e) undulating hair shaft contour under light microscopy, and (f) healthy control with straight hair shaft contour. (g)-(i) photographs of proband II:4 and (j)-(l) of proband II-3

Brain MRI, ultrasound examination of the abdomen, and EEG were normal. She had a small atrial septal defect and a minimal patent ductus arteriosus. Dental examination was unremarkable. Mild hyperopia was noted. At diagnosis of GH deficiency, the insulin-like growth factor 1 (IGF-1) level was <9.9 ng/ml (reference value: 15 to 191 ng/ml). The nocturnal (3.1 ng/mL) and clonidine-stimulated (4.9 ng/ml) GH levels were low. She responded well to GH treatment, with good catch-up growth and elevated IGF-1 levels.For all patients, karyotype and array comparative genomic hybridization (Agilent 244 K) were normal. Their hair was brittle, sparse, rough, and uncombable, with a shiny "cotton candy" appearance. The hair shafts displayed longitudinal grooves (pili canaliculi) on scanning electron microscopy. Polarizing and light microscopy showed tiger tail banding and hair shaft abnormalities typical of TTD (Figure 1(b)-(e)).

5 | DISCUSSION

The *MPLKIP*-gene encodes a 179 amino-acid protein comprising two exons. Its function is largely unknown, although it has been suggested to play a role in the maintenance of cell cycle integrity, and in regulating mitosis and cytokinesis (Nakabayashi, 2005; Zhang, 2007). It is expressed in numerous tissues; in situ RNA hybridization showed *MPLKIP* expression in epidermis and hair follicles of human fetal

fibroblasts, consistent with the TTD phenotype (Nakabayashi, 2005). Among the pathogenic *MPLKIP*-variants causing TTD4 (Table 1), most are protein-truncating, like the variant in our patients.

To evaluate genotype–phenotype relationships in TTD4, we compared clinical features among patients with MPLKIP-variants published to date (Table 1). In line with earlier reports, we observed no genotype–phenotype correlations (Botta, 2007; La Serna-Infantes, 2018). As is evident from Table 1, TTD4 is a multisystem disorder. For unknown reasons, most patients have shown growth retardation. Our patient had growth-hormone deficiency, which is, to the best of our knowledge, not described before in TTD4, although reported occasionally in photosensitive TTD (Atkinson, 2014). Although no distinct facial gestalt has been described, facial dysmorphism is frequently reported in TTD4.

In summary, we report three Finnish patients in two families with a novel variant in *MPLKIP* causing TTD4. This report adds to the literature by expanding the allelic and phenotypic spectra of this ultra-rare disorder.

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CONFLICT OF INTEREST

The authors report no financial or other conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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