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

Sonja Strang-Karlsson⁴ | Maria von Willebrand³ | Kristiina Avela² | Carina Wallgren-Pettersson⁴

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 TARSI 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.

Received: 17 November 2020 | Revised: 27 January 2021 | Accepted: 26 February 2021
DOI: 10.1002/ajmg.a.62168

© 2021 The Authors. American Journal of Medical Genetics Part A published by Wiley Periodicals LLC.
| 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 | Developmental delay | Microcephaly |
|-----------|-----------------------------|-----------------------------|-----------------------------|----------------|----------|--------|-----------------------------------|-------------------|-----------|
| Heller et al., 2015 | Caucasian | 1 | 14 | c.2T>G, p.(Met1Arg) | CMPD | - | - | + | N/A |
| Heller et al., 2015 | Caucasian | 1 | 4 | c.227delG, p. (Gly76Alafs*77) | CMPD | - | + | + | N/A |
| Heller et al., 2015 | Caucasian | 2 (1) | 1-2 | c.277delT, p. (Ser93Profs*60) | CMPD | - | + | + | N/A |
| 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 | Italy | 1 | 4 | c.148_152delCACAC, p(His50Alafs*8) | HMZ | - | + | + | N/A |
| | Italy | 1 | 3 | c.277delT, p. (Ser93Profs*60) | CMPD | + | + | + | + |
| | Italy | 1 | 8 | 11-30 kb whole gene deletion | HMZ | Reduced | + | + | N/A |
| | The Netherlands | 1 | 3 | c.277delT, p. (Ser93Profs*60) | HMZ | - | + | + | N/A |
| | Kuwait (Indian) | 1 | 3 | - 150kb whole gene deletion | HMZ | - | + | + | N/A |
| | Indian | 1 | 6 | c.229delC, p. (Arg77Glyfs*76) | HMZ | - | + | + | N/A |
| 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 | Developmental delay | Microcephaly |
|-----------------------------------|------------------------------|-------------------------------|------------------------------|-------------------|--------------|--------|----------------------------------------|----------------------|--------------|
| 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. (Thr169Asns*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              | Turkey                       | 1                             | N/A                          | c.505dupA, p. (Thr169Asns*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                          | Dysmorphic hair | Nail dystrophy | Skin abnormality | DVM features | Gonadal dysfunction | Tiger tail patterna | Hair shaft abnormality, otherb | 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 | + | Spasticity, hypoplasia of the frontal lobes |
| 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)  |
| Reference | Dysmorphic hair | Nail dystrophy | Skin abnormality | Dysmorphic features | Gonadal dysfunction | Tiger tail pattern<sup>a</sup> | Hair shaft abnormality, other<sup>b</sup> | Cardiac abnormality | Recurrent infections | Other |
|-----------|----------------|----------------|------------------|---------------------|---------------------|---------------------|-------------------------------|-------------------|------------------|--------|
| Nakabayashi et al., 2005; Przedborski et al., 1990 | + | – | – | + | + | + | N/A | – | – | Osteopenia |
| Nakabayashi et al., 2005; Rizzo et al., 1992 | + | + | – | N/A | Decreased fertility | + | + | N/A | – | Hypopituitarism 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 | – | 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 | – | Decreased sulfur content of hair in some |
| Shah et al., 2016 | + | + | – | N/A | Mitral regurgitation, all cases | + | N/A | – | – | Dental and ocular abnormalities, epilepsy |
| Pollitt et al., 1968 | + | + | Dry skin | N/A | N/A | N/A | – | N/A | – | Originally called Pollitt syndrome |
| Swagemakers et al., 2014 | + | + | Ichthyosis | + | N/A | – | N/A | – | – | 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 | + | N/A | Xerosis | m | + | + | + | 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<sup>c</sup> | N/A | N/A | Ichthyosis | + | Hypogonadism | + | N/A | N/A | – | – | – |
| N/A | N/A | Ichthyosis | + | Hypogonadism | + | N/A | N/A | – | – | – |
| N/A | N/A | Ichthyosis | + | Hypogonadism | + | N/A | N/A | – | – | – |
| Pande et al., 2020 | + | + | Ichthyosis | + | + | + | + | – | – | Childhood epilepsy, stereotypic hand movements |
| Current study | + | + | + | + | + | + | + | – | – | 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.

<sup>a</sup>Tiger tail appearance under polarizing light microscopy.

<sup>b</sup>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), trichoschisis (clean transverse fracture) and trichorrhexis nodosa-like fractures.

<sup>c</sup>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 (Vario, 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 started walking at age 20 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 head size 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.

At examination, epicantus, 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 kyphosis, 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 hypoplasia 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 head size 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, epicantus, 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.
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.

ACKNOWLEDGMENTS
The late Docent Mirja Somer is warmly remembered and thanked for inspiration and support in recognizing, 12 years ago that this was a recessively inherited clinical entity with discernible dysmorphic features and a likely founder variant in this particular subpopulation. We thank the patients and their parents for allowing the publication of their data. CENTOGENE is gratefully acknowledged for identifying the variant and for kindly providing us with technical data during manuscript preparation.

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.

ORCID
Sonja Strang-Karlsson https://orcid.org/0000-0002-8594-2077

REFERENCES
Atkinson, E. C., Thiara, D., Tamura, D., DiGiovanna, J. J., Kraemer, K. H., & Hadigan, C. (2014). Growth and nutrition in children with trichothiodystrophy. Journal of Pediatric Gastroenterology and Nutrition, 59(4), 458–464. https://doi.org/10.1097/MPG.0000000000000458
Baden, H. P., Jackson, C. E., Weiss, L., Jimbow, K., Lee, L., Kubilus, J., & Gold, R. J. (1976). The physicochemical properties of hair in the BIDS syndrome. American Journal of Human Genetics, 28(5), 514–521.
Botta, E., Offman, J., Nardo, T., Ricotti, R., Zambruno, G., & Sansone, D. (2007). Mutations in the C7orf11 (TTDN1) gene in six nonphotosensitive trichothiodystrophy patients: No obvious genotype-phenotype relationships. Human Mutation, 28(1), 92–96. https://doi.org/10.1002/humu.20419
Heller, E. R., Khan, S. G., Kuschal, C., Tamura, D., DiGiovanna, J. J., & Kraemer, K. H. (2015). Mutations in the TTDN1 gene are associated with a distinct trichothiodystrophy phenotype. Journal of Investigative Dermatology, 135(3), 734–741. https://doi.org/10.1038/jid.2014.440
Jackson, C. E., Weiss, L., & Watson, J. H. (1974). "Bristle" hair with short stature, intellectual impairment and decreased fertility: An autosomal recessive syndrome in an Amish kindred. Pediatrics, 54(2), 201–207.
Kalayci, T., Altunoglu, U., Karaman, B., Uyguner, Z., & Kayseril, H. (2019). Clinical and molecular findings of seven Turkish nonphotosensitive trichothiodystrophy patients with two novel mutations in MPLKIP. Abstracts from the 50th European Society of Human Genetics Conference-Posters. European Journal of Human Genetics, 26(Suppl 1), 113–819.
La Serna-Infantes, J., Pastor, M. C., Trubynkova, M., Velásquez, F. C., Sotomayor, F. V., & Barriga, H. A. (2018). Novel contiguous gene deletion in Peruvian girl with Trichothiodystrophy type 4 and glutaric aciduria type 3. European Journal of Medical Genetics, 61(7), 388–392. https://doi.org/10.1016/j.ejmg.2018.02.004
Liang, C., Kraemer, K. H., Morris, A., Schiffmann, R., Price, V. H., Menehee, E., & DiGiovanna, J. J. (2005). Characterization of tiger-tail banding and hair shaft abnormalities in trichothiodystrophy. American Journal of Human Genetics, 76(5), 510–516. https://doi.org/10.1086/428141
Pande, S., Shukla, A., & Girisha, K. M. (2020). Trichothiodystrophy type 4 in an Indian family. American Journal of Medical Genetics, 182(10), 2226–2229. https://doi.org/10.1002/ajmg.a.61794
Pode-Shakked, B., Marek-Yagel, D., Greenberger, S., Pode-Shakked, N., Pras, E., Barzilai, A., Yassim, S., Sidi, Y., & Anikster, Y. (2015). A novel mutation in the C7orf11 gene causes nonphotosensitive trichothiodystrophy in a multiplex highly consanguineous kindred. European Journal of Medical Genetics, 58(12), 685–688. https://doi.org/10.1016/j.ejmg.2015.10.012
Pollitt, R. J., Jenner, F. A., & Davies, M. (1968). Sibs with mental and physical retardation and trichorhhexis nodosa with abnormal amino acid composition of the hair. Archives of Disease in Childhood, 43(228), 211–216. https://doi.org/10.1136/adc.43.228.211
Prezdborski, S., Ferster, A., Goldman, S., Wolter, R., Song, M., Tonnesen, T., Pollitt, R. J., & Vamos, E. (1999). Trichothiodystrophy, mental retardation, short stature, ataxia, and gonadal dysfunction in three Moroccan siblings. American Journal of Medical Genetics, 35(4), 566–573. https://doi.org/10.1002/ajmg.1320350424
Richards, S., Aziz, N., Bale, S., Bick, D., Das, S., Gastier-Foster, J., Grody, W. W., Hegde, M., Lyon, E., Spector, E., Voelkerding, K., Rehm, H. L., & ACMG Laboratory Quality Assurance Committee. (2015). Standards and guidelines for the interpretation of sequence variants: A joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genetics in Medicine, 17, 405–424. https://doi.org/10.1038/gim.2015.30
Rizzo, R., Pavone, L., Micali, G., Calvieri, S., & Di Gregorio, L. (1992). Trichothiodystrophy: Report of a new case with severe nervous system impairment. Journal of Child Neurology, 7(3), 300–303. https://doi.org/10.1177/088307389200700311
Shah, K., Ali, R. H., Ansar, M., Lee, K., Chishti, M. S., Abbe, I., Li, B., University of Washington Center for Mendelian Genomics, Smith, J. D., Nickerson, D. A., Shendure, J., Cacock, P. J., Steyaert, W., Bamshad, M. J., Santos-Cortez, R. L. P., Leal, S. M., & Ahmad, W. (2016). Mitral regurgitation as a phenotypic manifestation of nonphotosensitive trichothiodystrophy due to a splice variant in MPLKIP. BMC Medical Genetics, 17, 13. https://doi.org/10.1186/s12881-016-0275-5
Swagemakers, S. M. A., Jaspers, N. G. J., Raams, A., Heijsman, D., Vermeulen, W., Troelstra, C., Kremer, A., Lincoln, S. E., Tearle, R., Hoeijmakers, J. H. J., & van der Spek, P. J. (2014). Pollitt syndrome patients carry mutation in TTDN1. Meta Gene, 2, 616–618. https://doi.org/10.1016/j.mgene.2014.08.001

Theil, A. F., Botta, E., Raams, A., Smith, D. E. C., Mendes, M. I., Caligiuri, G., Giachetti, S., Bione, S., Carriero, R., Liberi, G., Zardoni, L., Swagemakers, S. M. A., Salomons, G. S., Sarasin, A., Lehmann, A., van der Spek, P. J., Ogi, T., Hoeijmakers, J. H. J., Vermeulen, W., & Orioli, D. (2019). Bi-allelic TARS mutations are associated with brittle hair phenotype. American Journal of Human Genetics, 105(2), 434–440. https://doi.org/10.1016/j.ajhg.2019.06.017

Trujillano, D., Bertoli-Avellà, A. M., Kandaswamy, K. K., Weiss, M. E. R., Köster, J., Marais, A., Paknia, O., Schröder, R., García-Aznar, J. M., Werber, M., Brandau, O., del Castillo, M. C., Baldi, C., Wessel, K., Kishore, S., Nahavandi, N., Eyaid, W., Al Rifai, M. T., Al-Rumayyan, A., ... Jamra, R. A. (2017). Clinical exome sequencing: results from 2819 samples reflecting 1000 families. European Journal of Human Genetics, 25(2), 176–182. https://doi.org/10.1038/ejhg.2016.146

Varilo, T., Savukoski, M., Norio, R., Santavuori, P., Peltonen, L., & Järvelä, I. (1996). The age of human mutation: Genealogical and linkage disequilibrium analysis of the CLN5 mutation in the Finnish population. American Journal of Human Genetics, 58(3), 506–512.

Zhang, Y., Tian, Y., Chen, Q., Chen, D., Zhai, Z., & Shu, H.-B. (2007). TTDN1 is a Plk1-interacting protein involved in maintenance of cell cycle integrity. Cellular and Molecular Life Sciences, 64(5), 632–640. https://doi.org/10.1007/s00018-007-6501-8

Zhou, Y., Yang, X., Cao, Y., Su, H., Liu, L., Liang, L., & Zheng, Y. (2018). A homozygous G insertion in MPLKIP leads to TTDN1 with the hypogonadotropic hypogonadism symptom. BMC Medical Genetics, 19 (Suppl 1), 214. https://doi.org/10.1186/s12881-018-0723-5

How to cite this article: Strang-Karlsson S, von Willebrand M, Avela K, Wallgren-Pettersson C. A novel MPLKIP-variant in three Finnish patients with non-photosensitive trichothiodystrophy type 4. Am J Med Genet Part A. 2021; 185A:1875–1882. https://doi.org/10.1002/ajmg.a.62168