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A Rare Contiguous Gene Deletion Leading to Trichothiodystrophy Type 4 and Glutaric Aciduria Type 3

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Established Facts

- Homozygous or compound heterozygous mutations in *MPLKIP* and *SUGCT* genes, located on chromosome 7p14, cause trichothiodystrophy type 4 and glutaric aciduria type 3, respectively.
- Trichothiodystrophy type 4 is a rare disease characterized by growth retardation, microcephaly, developmental delay, ocular anomalies, and cutaneous abnormalities, such as brittle hair, ichthyosis, and nail dysplasia, whereas glutaric aciduria type 3 has not been associated with any known specific phenotype.

Novel Insights

- Contiguous gene syndromes should be considered in patients with coexisting distinct phenotypes; also homozygous copy number variations should be kept in mind, especially when there is parental consanguinity.

Keywords
Trichothiodystrophy type 4 · Glutaric aciduria type 3 · Microarray analysis · Contiguous gene deletion · Hypertransaminasemia

Abstract
Introduction: Trichothiodystrophy type 4 and glutaric aciduria type 3 are rare autosomal recessive disorders caused by biallelic variants in the *MPLKIP* and *SUGCT* genes on chromosome 7p14, respectively. Trichothiodystrophy type 4 is characterized by neurologic and cutaneous abnormalities. Glutaric aciduria type 3 is a rare metabolic disorder with inconsistent phenotype and elevated urinary excretion of glutaric acid. ***Case Presentation:*** Here, we report on an infant presenting with hypotonia, failure to thrive, microcephaly, dysmorphic features, brittle hair, hypertransaminasemia, and recurrent lower respiratory tract infections. Microarray analysis revealed a homozygous microdeletion involving the *MPLKIP* and *SUGCT* genes, which are located close to each other. ***Conclusion:*** Copy number variations should be considered in patients with coexisting clinical expression of dif-

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ferent genetic alterations. To the best of our knowledge, our patient is the second case with co-occurrence of trichothiodystrophy type 4 and glutaric aciduria type 3, resulting from a contiguous gene deletion.

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Introduction

Trichothiodystrophy type 4 (TTD4; MIM 234050), also called nonphotosensitive trichothiodystrophy 1, is a rare autosomal recessive disorder caused by mutations in the M-phase specific PLK1-interacting protein gene (*MPLKIP*; MIM 609188), which is located on chromosome 7p14. TTD4 is characterized by dry and brittle hair, intellectual disability, developmental delay, facial dysmorphism, microcephaly, short stature, decreased fertility, and susceptibility to respiratory infections [Faghri et al., 2008]. The *MPLKIP* gene, encoding the M-phase specific PLK1-interacting protein, is widely expressed in epidermis, hair follicles, brain, heart, liver, kidney, skeletal muscle, pancreas, lung, and placenta; however, its function is not fully understood [Nakabayashi et al., 2005; Winkles and Alberts, 2005]. Glutaric aciduria type 3 (GA3) is generally considered as a benign condition caused by biallelic mutations in the succinyl-CoA:glutarate-CoA transferase gene (*SUGCT*; MIM 609187) on chromosome 7p14 [Sherman et al., 2008]. Here, we present a male patient with a homozygous microdeletion of 83 kb in chromosome 7 encompassing both genes *MPLKIP* and *SUGCT*.

Case Presentation

A 4-month-old boy of consanguineous healthy parents was admitted to our clinic with ongoing hypertransaminasemia and recurrent lower respiratory tract infections (LRTIs). He was born at full term after an uneventful pregnancy and delivery with a birth weight of 2,900 g. He was the third live-born child of first cousin parents, and there was no marked family history about genetic dis-

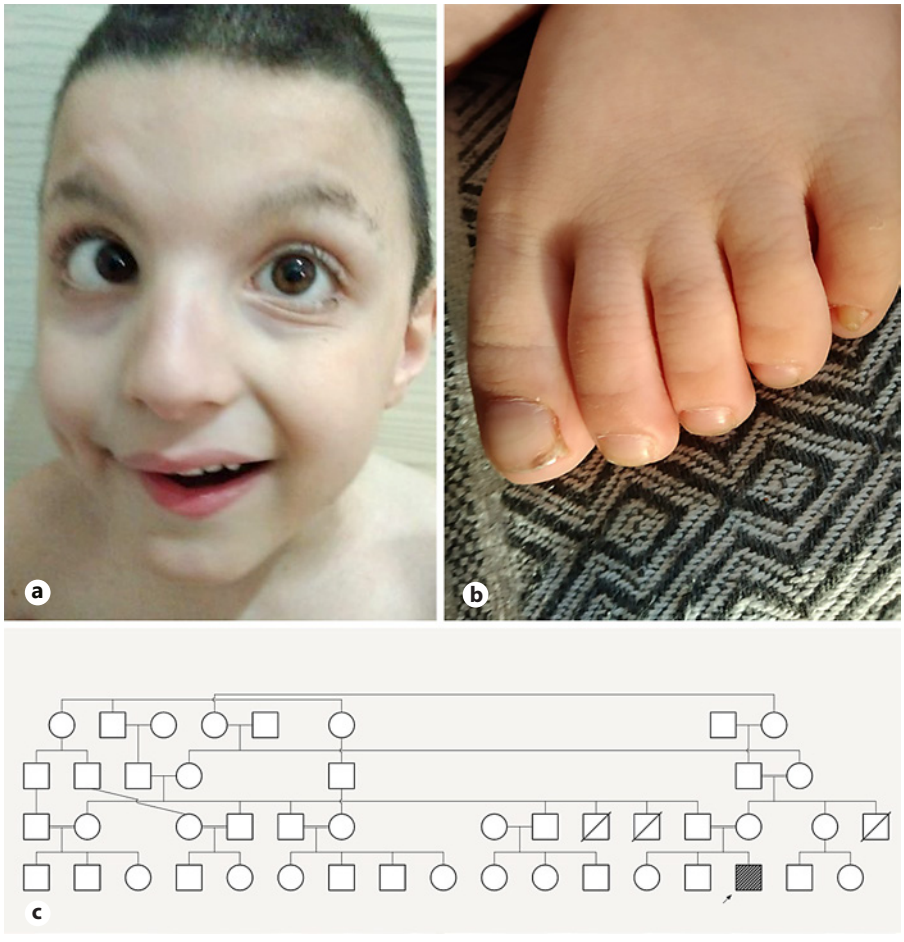


Fig. 1. Face (**a**) and foot (**b**) photographs of the patient and pedigree of the family (**c**). Please note woolly, coarse, and sparse hair on the scalp, eyebrows, and eyelashes, strabismus, and dystrophic toenails.

Table 1. Laboratory and investigation results at admission and follow-up

	Age, months		
	4	12	31
White blood cells, $\times 10^9$/L	7.79 (6–17)	4 (6–17)	9.19 (4–15.5)
Hemoglobin, g/dL	10.5 (10.5–14)	11.6 (10.5–14)	13.2 (11.5–14.5)
Platelets, $\times 10^9$/L	474 (84–478)	394 (84–478)	280 (150–450)
Total bilurubin, mg/dL	0.12 (<2)	0.11 (<2)	0.16 (<1.5)
Direct bilirubin, mg/dL	0.05 (<0.2)	0.06 (<0.2)	0.06 (<0.2)
Alanine aminotransferase, U/L	**96** (12–45)	**165** (12–45)	35 (5–55)
Aspartate aminotransferase, U/L	**103** (9–80)	**75** (9–80)	46 (20–60)
Gama glutamil transferase, U/L	**102** (8–90)	21 (5–32)	7 (5–32)
Creatine kinase, U/L	80 (5–200)	76 (5–200)	
Alkaline phosphatase, U/L	327 (150–420)	275 (150–420)	231 (100–420)
Albumin, g/dL	3.5 (1.9–4.9)	3.4 (1.9–4.9)	4.3 (3.4–5.2)
International normalized ratio		1.1 (0.8–1.29)	
Prothrombin time, s		12.2 (10–15)	
Hepatitis A antibody		Negative	
Hepatitis B surface antigen		Negative	
Hepatitis C virus antibody		Negative	
HIV antibody		Negative	
Anti-toxoplasma IgM		Negative	
Anti-cytomegalovirus IgM/Ig G		Negative	
Anti-rubella IgM		Negative	
Anti-Epstein Barr IgM		Negative	
Serum alpha1-antitrypsin, g/L		0.901	
Ferritin, ng/mL	282 (50–200)	32.4 (7–140)	
Ceruloplasmin, g/L		0.35 (>0.20)	
Urinary and blood amino acid patterns	Normal		
Carnitine and acylcarnitine profile	Normal		
Organic acids urine test profile	**Glutaric acid level was 7.3× higher than upper limit of normal**		
Very long chain fatty acids profile	Normal		
Alpha fetoprotein, ng/mL		37.8 (0.8–87)	3.02 (0.8–87)
Immunoglobulin A, g/L		0.501 (0.09–0.7)	
Immunoglobulin G, g/L		7.6 (2.9–7.7)	
Anti-tissue transglutaminase IgA		Negative	
Anti-nuclear antibody		Negative	
Anti-smooth muscle antibody		Negative	

Table 1 (continued)

	Age, months		
	4	12	31
Liver/kidney microsome type 1 antibody		Negative	
Hepatobiliary and portal system doppler ultrasound		**Increased echogenicity of the liver parenchyma**	normal
Detailed eye examination		normal	
Liver biopsy		**Minimal steatosis and inflammation, reactive hepatocellular reaction with negative PAS staining**	

Values in parentheses represent normal reference ranges. Values that lie outside the laboratory reference ranges are indicated in bold. PAS, periodic acid-Schiff.

orders (Fig. 1). He had been hospitalized twice due to cyanosis and respiratory distress before admission to our clinic.

On admission, he was malnourished: weight 5.2 kg (−2.81 SD), length 61 cm (−1.71 SD), and occipitofrontal circumference 39 cm (−2.41 SD). Physical examination revealed woolly, sparse, and brittle hair, sparse and coarse eyebrows/eyelashes, dystrophic toenails, high-arched palate, strabismus, poor head control, and hypotonia on horizontal and vertical suspension (Fig. 1).

His routine laboratory tests were normal except for mildly elevated liver enzymes. Laboratory and other investigation results for high liver enzyme tests are summarized in Table 1.

Silent microaspirations caused by the dysfunction of the pharyngeal phase of swallowing were detected with videofluoroscopy. Transthoracic echocardiography showed contrast medium passing through the patent foramen ovale, and a cranial MRI revealed inferior vermis hypoplasia and large cisterna magna. Microscopic analysis of the hair shaft showed thick and weak nodes (trichorrhexis nodosa).

Conventional cytogenetic studies demonstrated a normal 46,XY karyotype. Trichohepatoenteric syndrome and Menkes disease were excluded after sequencing analysis of *TTC37* and *ATP7A*. Microarray analysis revealed a homozygous microdeletion of 83 kb in chromosome 7 (arr[GRCh38] 7p14.1(40,116,025_40,199,047)×0), encompassing the genes *MPLKIP* and *SUGCT* (Fig. 2). The homozygous microdeletion involving 2 protein-coding genes related to recessive conditions is classified as pathogenic according to ACMG guidelines [Kearney et al., 2011]. The parents were also heterozygous carriers of this microdeletion. Written informed consent was obtained from the family before the genetic tests.

After administration of enteral tube feeding (ETF), aspiration-related recurrent hospitalizations started to decrease gradually. He consistently grew between 10th and 25th percentile for height and weight after the first year of tube feeding. On his recent admission at the age of 3 years, his height was 94 cm (−0.56 SD) and weight 13.5 kg (−0.65 SD). During 3 years of follow-up, developmental delay and intellectual disability became more apparent. He achieved head control at 16 months of age and started to sit without support at 26 months of age. At the age of 3 years, he was able to speak only a few rudimentary words, showed new onset repetitive behavior such as head banging, but had a sociable and friendly personality. His liver enzyme tests returned to normal ranges on follow-up, but swallowing problems with liquids continue.

Methods

A genomic DNA sample was extracted from peripheral blood lymphocytes of the patient using the salt precipitation method. The microarray was performed using Illumina Infinium CytoSNP-850K BeadChip array platform (Illumina, USA) according to the manufacturer's instructions. The data were analyzed using the BlueFuse Multi Analysis Software. Copy number variations detected in the patient were interpreted by comparing with inhouse data and using public databases, such as Database of Chromosomal Imbalance and Phenotype in Humans using Ensemble Resources (DECIPHER), Database of Genomic Variants (DGV), Online Mendelian Inheritance in Man (OMIM), and ClinVar Variants.

Discussion

Trichothiodystrophy is a rare autosomal recessive disorder characterized by a main phenotype involving cutaneous abnormalities, intellectual disability, and growth failure. Patients with TTD4 have heterogenous clinical findings including brittle hair with a tiger-tail pattern, failure to thrive, developmental delay, intellectual disability, axial hypotonia, seizures, poor motor control, recurrent infections, hypergonadotropic hypogonadism, short stature, and osteoporosis [Heller et al., 2015; Pode-Shakked et al., 2015; Shah et al., 2016]. Also, mitral regurgitation and severe renal failure were reported with different mutations in *MPLKIP* [Pode-Shakked et al., 2015; Shah et al., 2016].

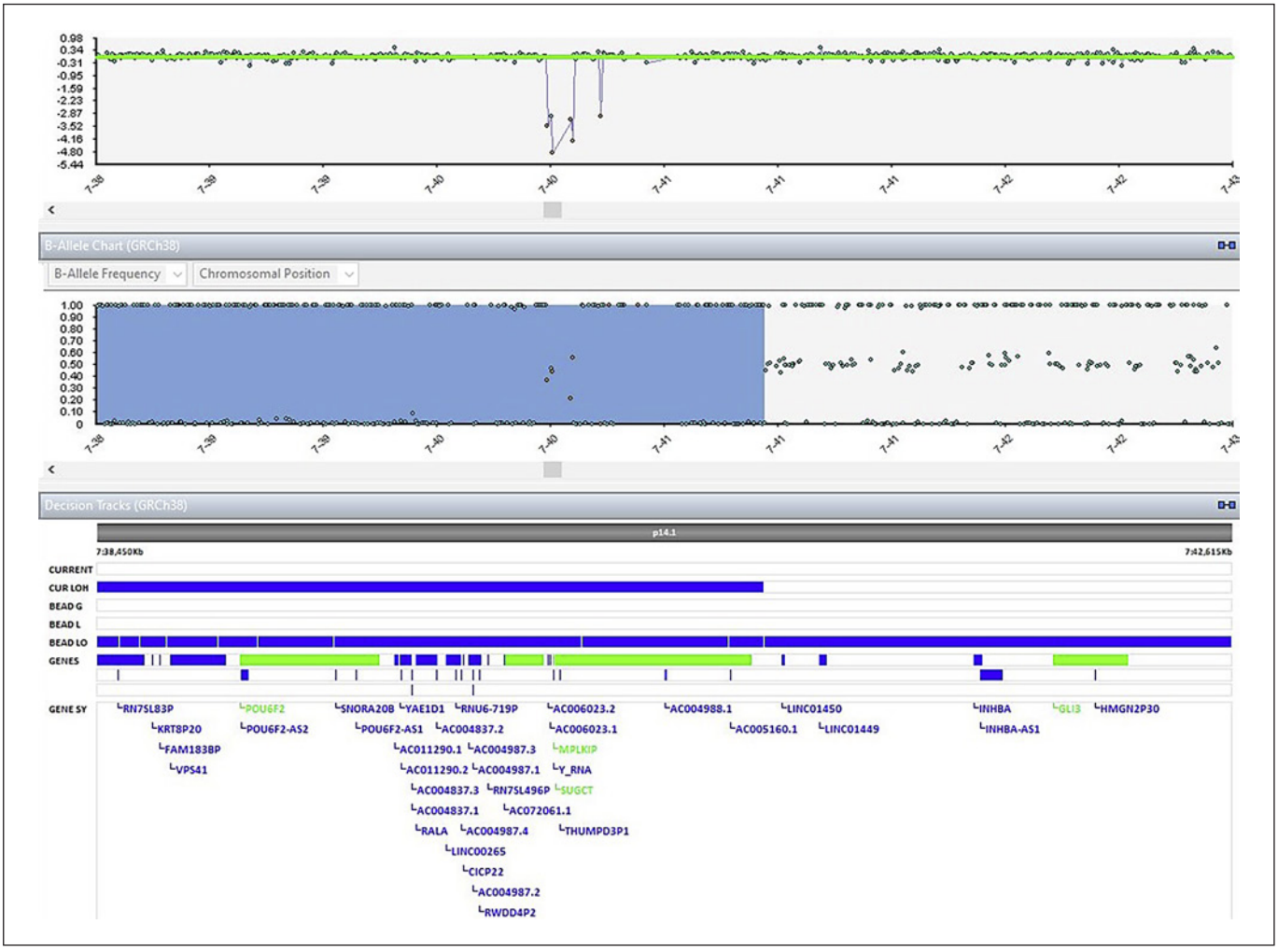


Fig. 2. Microarray analysis showing a homozygous microdeletion of 83 kb in chromosome 7 spanning the genes *MPLKIP* and *SUGCT*.

The *MPLKIP* gene encodes a protein interacting with polo-like kinase 1 (PLK1) which has a role in cell cycle regulation and gene transcription [Nakabayashi et al., 2005; Zhang et al., 2007]. However, no robust genotype-phenotype correlation was established [Botta et al., 2007].

GA3 is caused by homozygous and compound heterozygous mutations in the *SUGCT* gene (*C7orf10*) on chromosome 7p14. *SUGCT* encodes succinate-hydroxymethylglutarate CoA-transferase that converts glutarate to glutaryl-CoA [Marlaire et al., 2014]. Patients remain largely asymptomatic despite high levels of glutaric acid in the urine. Our patient's glutaric acid level was found to be 7.3× higher than upper limits of normal in urine organic acid analysis.

The first case who had a contiguous gene deletion resulting in TTD4 and GA3 was described from Peru [La Serna-Infantes et al., 2018]. To the best of our knowledge, our patient is the second case with a similar contiguous gene deletion. The Peruvian TTD4 patient had nystagmus, scoliosis, brachydactyly, and tooth abnormality, which are different from our patient (Table 2).

Findings like trichorrhexis nodosa, microcephaly, dysmorphic features, short stature, hypotonia, strabismus, developmental delay, intellectual disability, repetitive behavior, friendly personality, inferior vermis hypoplasia, osteoporosis, and recurrent lower respiratory tract infections, which are the hallmarks of TTD4, were also seen in our patient [Heller et al., 2015; Pode-Shakked et al., 2015; Shah et al., 2016; La Serna-Infantes et al.,

Table 2. Comparison of the clinical findings of the present patient with the patient previously reported along with the findings of TTD4 and GA3

	Present patient	Previously reported patient with TTD4 and GA3 [La Serna-Infantes et al., 2018]
Global developmental delay	+	+
Hypotonia	+	–
Short stature	+	+
Microcephaly	+	+
Dysmorphic features	Epicanthal folds; high-arched palate	Prematurely aged and asymmetric face with hypoplastic zygomatic arches; anteverted nares and thick nasal root; downslanting mouth corners
Skin findings	Woolly, sparse, and brittle hair; trichorrhexis nodosa; alopecic area; dystrophic toenails	Short, coarse, sparse and brittle hair; alopecic parietal area; trichorrhexis nodosa; café-au-lait macules; follicular keratosis; short, thin, and irregular nails of the fingers
Skeletal findings	Pes planus	Scoliosis; brachydactyly; clinodactyly of the 5th fingers; pes planovalgus
Eye findings	Strabismus	Nystagmus

2018]. Our patient also had aspirations due to impaired swallowing. After the admission of ETF, catch-up in terms of weight and height according to the age was achieved and recurrent LRTIs disappeared. Malnutrition and recurrent LRTIs, which are frequently reported in TTD4 patients, disappeared with ETF in our patient. Therefore, videofluoroscopic examinations should be kept in mind in TTD4 patients who are complicated with recurrent respiratory tract infections such as otitis media and pneumonia.

Despite detailed examination, the reason for the elevation of transaminases could not be explained. It has not been reported that TTD4 has such a hepatic finding. On the follow-up, the patient's liver enzyme levels returned to normal, and no additional liver disease findings were detected, so further evaluation was not performed. Transient liver enzyme elevation may be associated with the recurrent respiratory tract infections he suffered from and the usage of multiple medications.

We aim to emphasize the protective role of ETF for malnutrition and recurrent LRTIs in TTD4 patients. Homozygous copy number variations should be considered in patients with consanguineous families, and microarray analysis is an efficient diagnostic tool to uncover the underlying genetic etiology.

Statement of Ethics

This study was performed in accordance with the Declaration of Helsinki Principles. The patient's parents provided their written and informed consent for the publication of this case report and any accompanying images. Ethical approval was not required for this study in accordance with local/national guidelines.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

E. Demir, C. Tuna Kırsaçlıoğlu, F.T. Eminoğlu, Z. Kuloğlu, and A. Kansu constructed the idea for research and conceived the study. E. Demir and N. Doğulu collected clinical data. V. Topçu contributed to genetic analysis and interpreted the results. E. Demir wrote the manuscript. C. Tuna Kırsaçlıoğlu, F.T. Eminoğlu, Z. Kuloğlu, and A. Kansu critically reviewed and edited the work. All authors revised and approved the final version of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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