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CLINICAL REPORT

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Two cases of Legg–Perthes and intellectual disability in Tricho–Rhino–Phalangeal syndrome type 1 associated with novel *TRPS1* mutations

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Tricho–Rhino–Phalangeal syndrome is a rare autosomal dominant genetic disorder caused by mutations in the *TRPS1* gene. This malformation syndrome is characterized by distinctive craniofacial features including sparse scalp hair, bulbous tip of the nose, long flat philtrum, thin upper vermilion border, and protruding ears. Skeletal abnormalities include cone-shaped epiphyses at the phalanges, hip malformations, and short stature. In this report, we describe two patients with the physical manifestations and genotype of TRPS type I but with learning/intellectual disability not typically described as part of the syndrome. The first patient has a novel heterozygous two-base-pair deletion of nucleotides at 3198-3199 (c.3198-3199delAT) in the *TRPS1* gene causing a translational frameshift and subsequent alternate stop codon. The second patient has a 3.08 million base-pair interstitial deletion at 8q23.3 (113,735,487–116,818,578), which includes the *TRPS1* gene and *CSMD3*. Our patients have characteristic craniofacial features, Legg–Perthes syndrome, various skeletal abnormalities including cone shaped epiphyses, anxiety (first patient), and intellectual disability, presenting unusual phenotypes that add to the clinical spectrum of the disease.

KEYWORDS
cone shaped epiphyses, Legg–Perthes, Tricho–Rhino–Phalangeal syndrome type 1, *TRPS1*

1 | INTRODUCTION

Tricho–Rhino–Phalangeal syndrome (TRPS) is a rare autosomal dominant genetic disorder characterized by craniofacial dysmorphism and bone deformities, first described by Giedion (1966). There are three different types of TRPS: TRPS type I (OMIM #190350), TRPS type II (OMIM #150230), also known as Langer Giedion syndrome (LGS), and TRPS type III (OMIM #190351). Characteristic features of TRPS type I include sparse scalp hair, rounded nose, long flat philtrum, and thin upper lip. Individuals with TRPS type I often have short stature and skeletal abnormalities including cone-shaped epiphyses in the fingers and toes. TRPS type II is clinically differentiated from TRPS types I and III by the presence of exostoses, distinct facial features, and occasional intellectual disability (Candamourty, Venkatachalam, Karthikeyan, & Babu, 2012). Intellectual delay in TRPS type I is generally thought to mimic the frequency in the general population (Maas et al., 2015). Individuals with TRPS type III have features similar to those with type I, but additionally often have brachydactyly and are generally shorter in stature (Lüdecke et al., 2001). TRPS types I and III are caused by gross deletions on chromosome 8 between 8p23.3 and 8p24.13 and loss of function mutations of the *TRPS1* gene. In contrast, TRPS type II is caused by contiguous gene deletions involving both the *EXT1* and *TRPS1* genes (Ludecke et al., 1995), the *EXT1* gene contributing to exostoses.

In this report, we describe two patients affected with TRPS type I. The first patient described has a novel, heterozygous, two-base-pair deletion of nucleotides 3198-3199 (c.3198-3199delAT). This sequence variation results in a translational frameshift, leading to premature termination of protein translation and was predicted to be probably damaging and deleterious by PolyPhen and SIFT in silico

analyzes, respectively (Adzhubei et al., 2010; Kumar, Henikoff, & Ng, 2009). The second patient described has a 3.08 Mbp interstitial deletion at 8q23.3 identified by chromosomal microarray. This deletion includes the *TRPS1* gene and the *CSMD3* gene. *CSMD3* is associated with changes in brain activity, but loss of one copy is of uncertain significance.

2 | CLINICAL REPORTS

2.1 | Patient 1

We report a 20-year-old male who was previously diagnosed with Langer Giedion syndrome. He was born to a 27-year-old G2P1 mother following an unremarkable pregnancy and delivery. There were no unusual prenatal findings. His weight was 3.6 kg (50th centile), his length was (75–90th centile), and his head circumference was 38.1 cm (90th centile). Craniofacial features present at birth included macrocrania and a bulging fontanelle. In the neonatal period, he had hypotonia and cephalohematoma which resulted in hyperbilirubinemia requiring phototherapy treatment and acquired group B strep requiring a 2-week hospital stay.

Our patient's developmental and social history includes language and global developmental delay requiring special education classes, and speech and occupational therapy. He walked independently at 12 months; however, he did not say his first words until 3 years of age. He was reported to be socially immature and had rage-like episodes, obsessive-compulsive tendencies, short attention span and developmental and social delays throughout childhood. He was diagnosed with autism spectrum disorder and nonverbal learning disorder and his family was informed that his megaloencephalopathy was the cause of his delays. He had magnetic resonance imaging of the brain which revealed an extracranial group of tortuous vessels in the right posterior triangle of the neck. In adolescence our patient struggled with anxiety which was treated with clonazepam; however, he subsequently discontinued this medication because it caused suicidal ideation. Anxiety was not present in his family members and was attributed to his diagnosis of TRPS1.

At the age of 4 years he was diagnosed with Legg–Perthes disease (Figure 1E and F) and was treated with physical therapy and anti-inflammatory medicine to relieve the joint stiffness. His height and weight were on the 50th centile, however his head circumference increased to the 98th centile. As a child, our patient reports always having thin nails and sparse hair growth.

An X-ray at 9 years showed cone shaped epiphysis of the left hand and right fifth metacarpal; however, there was no evidence of exostoses (Figure 1G).

At 19 years of age, he sought a genetics evaluation in order to help him possibly qualify for special accommodations in college. His height was 165 cm (10th centile) and his weight was 68.9 kg (55th centile). His craniofacial features included a prominent nose with a bulbous nasal tip, prominent eyes, and small low set ears (Figure 1A and B). He has unusually angulated fingers with prominent joints and a short left index finger (Figure 1C), severe pronation, pes planus, and prominent second and third toes bilaterally (Figure 1D). His hand and foot measurements were in the normal range. Currently, at the age of 20 years, he reports mild to moderate pain in his hips and feet after walking excessively.

An SNP Microarray performed using the Affymetrix Cyloscan HD platform did not reveal a deletion on chromosome 8. *TRPS1* gene sequencing was then performed by amplifying and sequencing the full coding regions of the indicated exons as well as approximately 20 bases into the 5′ or 3′ ends of these exons. A novel heterozygous two-base-pair deletion of nucleotides 3198-3199 (c.3198-3199delAT)

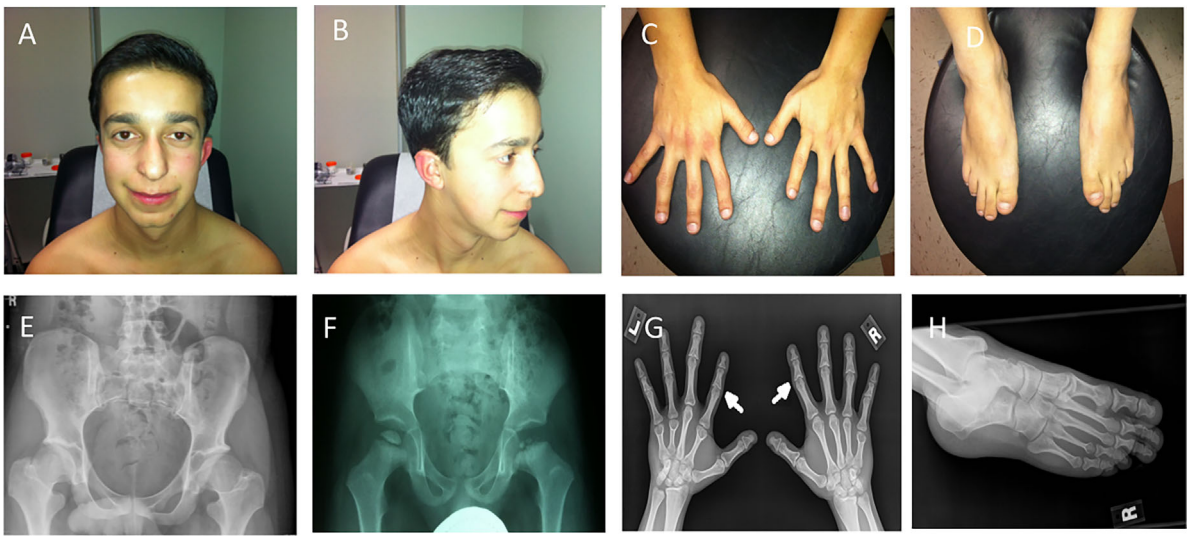

FIGURE 1 A: Case 1 reveals a prominent nose with a bulbous tip. B: Lateral view of the face revealing small, low-set ears. C: Dorsum of hands showing unusually angulated fingers with prominent joints D: Unusual feet with prominent 2nd and 3rd toes, and pes planus. E and F: X-rays of the hips showing progression of severe Legg–Perthes disease at ages 6 years and 20 years, respectively. G: X-rays of the hands showing cone shaped epiphysis of the phalanges at 20 years. H: X-rays of the feet showing prominent 2nd and 3rd toes, and cone shaped epiphyses at 20 years. [Color figure can be viewed at wileyonlinelibrary.com]

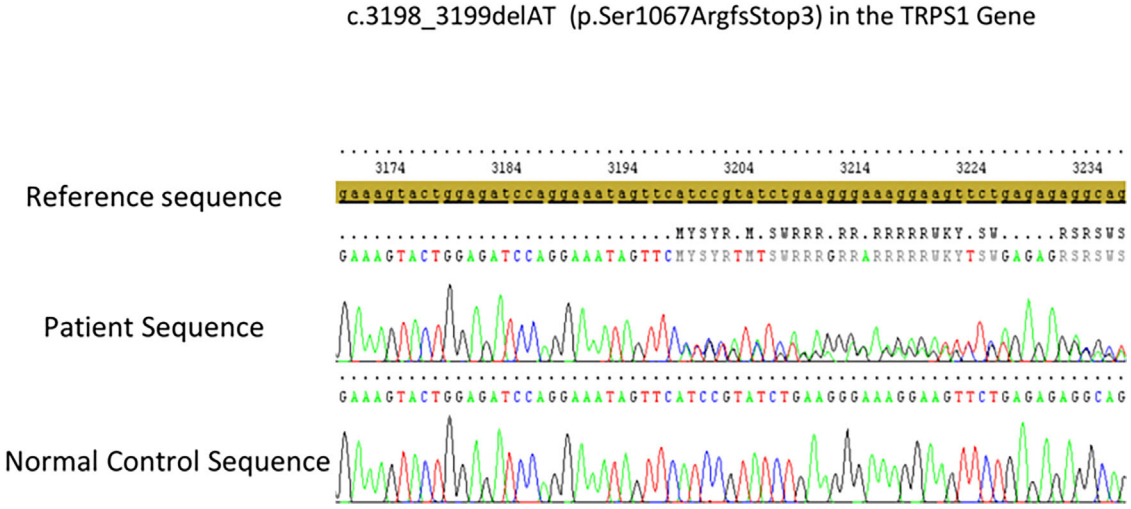

FIGURE 2 Chromatogram in patient 1 shows the two-base-pair deletion of nucleotides 3198-3199 (c.3198-3199delAT) in TRPS1 resulted in a novel translational frame shift and premature protein termination (p.Ser1067ArgfsStop3). [Color figure can be viewed at wileyonlinelibrary.com]

in *TRPS1* was identified. This deletion resulted in a novel translational frameshift and premature protein termination (p.Ser1067ArgfsStop3) (Figure 2). A separate sequence variant in the pre-coding region was identified; however, this variant was considered to be a benign polymorphism commonly found in healthy control individuals (reference number (rs35329862) in NCBI's SNP database).

The patient has no family history of TRPS1, and his parents who did not wish to pursue testing did not have any clinical manifestation of TRPS1, suggesting that the c.3198-3199delAT mutation is a de novo occurrence in him.

2.2 | Patient 2

This 14-year-old male was born to a 20-year-old G4P3>4 woman following an uncomplicated pregnancy and uncomplicated delivery. There were no suspected teratogen exposures and the union was not known to be consanguineous. At birth, length was 20 inches (69th centile), weight was 3.37 kg (58th centile), head circumference was 35.6 cm (82nd centile), and auditory testing resulted in referral to the county Early Intervention Program.

Like Patient 1, this patient had significant developmental delays when he was younger, walking at 3 years of age and speaking his first words at 4 years. He has made significant improvements with the aid of special education, and remains in special education classes. His Individualized Education Plan indicates that his performance on the Wechsler Intelligence Scale for Children, Fifth Edition is low-average to very low, and that his WIAT III standardized testing scores are mostly in the 70's, with an Oral Reading Fluency score at 62.

X-ray and MRI studies demonstrate avascular necrosis of the left femoral head, but no exostoses. At age 10 years, the patient was

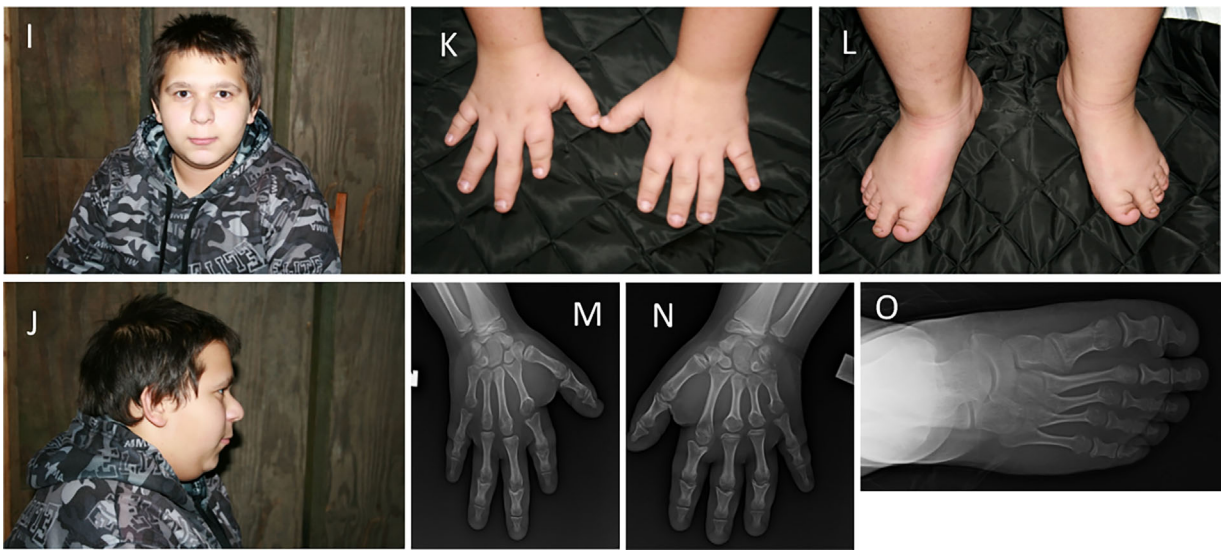

FIGURE 3 I: Case 2: Craniofacial features include a prominent nose with a bulbous tip J: Lateral image of face reveals retrognathia and low-set ears; K: Hand photographs reveal shortened index and fifth digits L: Feet reveal short polices bilaterally. M,N: X-rays of hands reveal short distal phalanges 1–4, short metacarpals 2 and 5. Wide and irregular MCP joints and cone shape of middle phalanx bases. O: X-rays of feet show a club shaped distal metatarsals with short lateral three rays bilaterally. Short distal phalanges of all toes are noted. [Color figure can be viewed at wileyonlinelibrary.com]

diagnosed with Osteochondrosis/Legg–Calve–Perthes disease of the left hip and gained 53 kg while immobile from the disease. He underwent left hip arthrodesis and spica casting surgery at age 13 years and remained hyperphagic after recovery.

This patient presented for genetic testing at age 14 years with short stature (height 143.5 cm, 1st centile), obesity (weight 71.5 kg, 96th centile), large tongue with prominent taste buds, high arched palate, mild scoliosis, and a bulbous nasal tip (Figure 3I). He had short hand and foot length (18.5 cm, 3rd centile), brachydactyly (middle finger length was 5.5 cm, less than 3rd centile), and cone shaped epiphyses (Figure 3K–O), as well as hypoplastic toenails. He also had a hypoplastic penis.

A SNP Microarray performed using the Affymetrix Cyloscan HD platform identified a 198 kbp deletion at 14q32.11 (90,294,697–90,492,781) and a 3.08 Mbp interstitial deletion at 8q23.3 (113,735,487–116,818,578) (Figures 4 and S1). Data was analyzed using the Chromosome Analysis Suite using the GRCh37/hg 19 assembly. The deletion at 8q23.3 includes the *TRPS1* gene and also includes CSMD3 (CUB and Sushi Multiple Domains Protein 3) which is associated with changes in brain activity, but loss of one copy is of uncertain significance. The deletion at 14q32.11 includes the genes TDP1 (tyrosyl-DNA phosphodiesterase) associated with autosomal recessive spinocerebellar ataxia with peripheral axonal motor and sensory neuropathy and *EFCAB11*. Deletions in single copies *TDP1* and *EFCAB11* were considered variants of uncertain significance and likely not affecting our patient's presentation.

The patient's father was reported to also be affected by short stature (147 cm, less than 3rd centile), early baldness, irregularly short digits, a bulbous nasal tip, and joint disease requiring bilateral hip replacement. We have not been able to test the parents for the *TRPS1* deletion, however his father is suspected of also having this deletion of TRPS.

3 | DISCUSSION

Our patients have many of the classical features of TRPS I including sparse scalp hair, a bulbous tip of the nose, a long flat philtrum, a thin upper vermilion border, protruding ears, short stature, angulated fingers with prominent joints, short left (patient 1) and right (patient 2) index fingers, prominent second and third toes bilaterally (patient 1 only), and cone-shaped epiphyses of the phalanges. Our patients also present with severe Legg–Perthes, which has previously been associated with TRPS in up to half of all patients (Dunbar, Sussman, & Aiona, 1995; Gaardsted, Hjøllund Madsen, & Friedrich, 1982; Minguella et al., 1993).

A current literature review however found no association between mutations in *TRPS1* and anxiety or suicidal ideation. Additionally, intellectual disability is most often associated with TRPS type II or other large deletions (Gonzalez-Huerta, Cuevas-Covarrubias, & Messina-Baas, 2007; Maas et al., 2015).

Lüdecke et al. (2001) analyzed the genotypic and phenotypic spectrum in TRPS types I and III and found one patient with severe intellectual disability and a large cytogenetically visible deletion, and other patients with mild intellectual disability with a variety of *TRPS1* mutations. Another study identified an individual with a novel two base pair heterozygous deletion (c.2304–2305delAG) in exon 5 of the *TRPS1* gene (Gonzalez-Huerta et al., 2007) and intellectual disability and microcephaly.

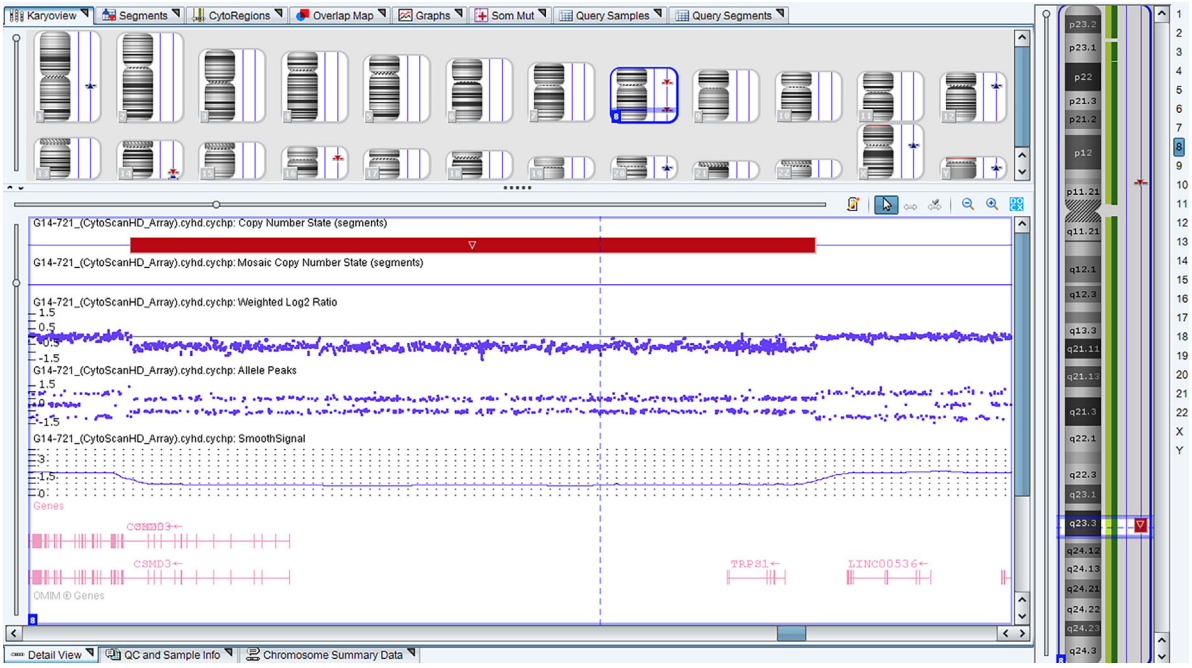

FIGURE 4 Chromosome 8 is depicted vertically on the right of the figure. The box around the q23.3 region in the vertical chromosome is displayed in the main segment of the figure in several different ways. The Copy Number State shows a deletion as a thick bar of 3,083 kbp. The Weighted Log2 Ratio shows a dip in the line of dots, which represents that there is only one copy of the genes in this region. The Allele Peaks show loss of heterozygosity when the lines progress from 3 lines to 2 lines in the area of the deletion. The SmoothSignal also shows that there is only one copy of the gene. The thin labeled lines at the bottom of the figure show the OMIM genes involved, CSMD3 and TRPS1. [Color figure can be viewed at wileyonlinelibrary.com]

The literature was reviewed in order to determine whether mutations in exon 7, the exon in which our first patient's mutation occurs, can be associated with intellectual disability and developmental delay. To date, approximately 79 pathogenic mutations in the *TRPS1* gene have been reported and eleven, in addition to the mutation being presented here, occur in exon 7 of the *TRPS1* gene (Hilton et al., 2002; Momeni et al., 2000). While it has been previously hypothesized that a *TRPS1* exon 7 mutation could result in a mild phenotype (Gentile, Fiorente, Buonadonna, Macina, & Cariola, 2003; Rossi et al., 2007), codon 952 in exon 7 has been identified as a mutation hotspot site and indeed studies have shown that mutations at this site may be associated with intellectual disability (Sidler et al., 2012).

The second patient described has learning disability that may be related to the deletion in *TRPS1* or due to unmasking heterozygosity in the *CSMD3* gene. *CSMD3* is a candidate gene for autism and psychomotor delay (Floris et al., 2008), is found in apical dendrites in hippocampal and pyramidal neurons and is thought to regulate dendrite development (Mizukami, Kohno, & Hattori, 2016).

In conclusion, we describe two patients with typical craniofacial and skeletal features of TRPS type I, severe Legg–Perthes and developmental delays and learning disability resulting from: (1) a novel heterozygous two-base-pair deletion of nucleotides 3198-3199 (c.3198-3199delAT) in the *TRPS1* gene, which results in a translational frameshift and leads to an alternate stop codon and (2) a 3.08 Mbp interstitial deletion at 8q23.3 (113,735,487–116,818,578) that includes the *TRPS1* and *CSMD3* genes.

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CONFLICT OF INTEREST

None of the authors have any conflicts of interest to disclose.

REFERENCES

Adzhubei, I. A., Schmidt, S., Peshkin, L., Ramensky, V. E., Gerasimova, A., Bork, P., ... Sunyaev, S. R. (2010). A method and server for predicting damaging missense mutations. *Nature Methods*, *7*(4), 248–249.

Candamourty, R., Venkatachalam, S., Karthikeyan, B., & Babu, M. R. (2012). Trichorhinophalangeal syndrome type 1: A case report with literature review. *Journal of Natural Science, Biology and Medicine*, *3*(2), 209–211.

Dunbar, J. D., Sussman, M. D., & Aiona, M. D. (1995). Hip pathology in the trichorhinophalangeal syndrome. *Journal of Pediatric Orthopaedics*, *15*(3), 381–385.

Floris, C., Rassu, S., Boccone, L., Gasperini, D., Cao, A., & Crisponi, L. (2008). Two patients with balanced translocations and autistic disorder: CSMD3 as a candidate gene for autism found in their common 8q23 breakpoint area. *European Journal of Human Genetics*, *16*(6), 696–704.

Gaardsted, C., Hjøllund Madsen, E., & Friedrich, U. (1982). A Danish kindred with tricho-rhino-phalangeal syndrome type I. *European Journal of Pediatrics*, *139*(1), 84–87.

Gentile, M., Fiorente, P., Buonadonna, A. L., Macina, F., & Cariola, F. (2003). A novel mutation in exon 7 in a family with mild tricho–rhino–phalangeal syndrome type I. *Clinical Genetics*, *63*(2), 166–167.

Giedion, A. (1966). Tricho-rhino-phalangeal syndrome. *Helvetica Paediatrica Acta*, *21*(5), 475–485.

Gonzalez-Huerta, L. M., Cuevas-Covarrubias, S. A., & Messina-Baas, O. M. (2007). Tricho-rhino-phalangeal type I syndrome and mental retardation: Identification of a novel mutation in the TRPS1 gene. *Journal of Dermatological Science*, *48*(1), 61–63.

Hilton, M. J., Sawyer, J. M., Gutiérrez, L., Hogart, A., Kung, T. C., & Wells, D. E. (2002). Analysis of novel and recurrent mutations responsible for the tricho-rhino-phalangeal syndromes. *Journal of Human Genetics*, *47*(3), 103–106.

Kumar, P., Henikoff, S., & Ng, P. C. (2009). Predicting the effects of coding non-synonymous variants on protein function using the SIFT algorithm. *Nature Protocols*, *4*(8), 1073–1081.

Ludecke, H. J., Wagner, M. J., Nardmann, J., La Pillo, B., Parrish, J. E., Willems, P. J., ... Horsthemke, B. (1995). Molecular dissection of a contiguous gene syndrome: Localization of the genes involved in the Langer-Giedion syndrome. *Human Molecular Genetics*, *4*(1), 31–36.

Lüdecke, H. J., Schaper, J., Meinecke, P., Momeni, P., Gross, S., Von Holtum, D., ... Christen, H. J. (2001). Genotypic and phenotypic spectrum in tricho-rhino-phalangeal syndrome types I and III. *American Journal of Medical Genetics*, *68*(1), 81–91.

Maas, S. M., Shaw, A. C., Bikker, H., Lüdecke, H. J., van der Tuin, K., Badura-Stronka, M., ... Cobben, J. (2015). Phenotype and genotype in 103 patients with tricho-rhino-phalangeal syndrome. *European Journal of Medical Genetics.*, May 31 *58*(5), 279–292.

Minguella, I., Ubierna, M., Escola, J., Roca, A., Prats, J., & Pintos-Morell, G. (1993). Trichorhinophalangeal syndrome, type I, with avascular necrosis of the femoral head. *Acta Paediatrica*, *82*(3), 329–330.

Mizukami, T., Kohno, T., & Hattori, M. (2016). CUB and Sushi multiple domains 3 regulates dendrite development. *Neuroscience Research*, *110*, 11–17.

Momeni, P., Glockner, G., Schmidt, O., von Holtum, D., Albrecht, B., Gillessen-Kaesbach, G., ... Ludecke, H.-J. (2000). Mutations in a new gene, encoding a zinc-finger protein, cause tricho-rhino-phalangeal syndrome type I. *Nature Genetics*, *24*(1), 71–74.

Rossi, A., Devirgiliis, V., Panasiti, V., Borroni, R. G., Carlesimo, M., Gentile, M., ... Calvieri, S. (2007). Missense mutation in exon 7 of TRPS1 gene in an Italian family with a mild form of trichorhinophalangeal syndrome type I. *British Journal of Dermatology*, *157*(5), 1021–1024.

Sidler, J. A., Filges, I., Boesch, N., Ramelli, G. P., Röthlisberger, B., Huber, A. R., ... Heinimann, K. (2012). TRPS1 codon 952 constitutes a mutational hot spot in trichorhinophalangeal syndrome type I and could be associated with intellectual disability. *Clinical Dysmorphology*, *21*(2), 87–90.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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