Acta Dermatovenerol APA

Acta Dermatovenerologica
Alpina, Pannonica et Adriatica

2022;31:43-46
doi: 10.15570/actaapa.2022.6

Trichorhinophalangeal syndrome: a case report and brief literature review

Oriana Simonetti[1]✉*, Giulia Radi[1*], Elisa Molinelli[1], Federico Diotallevi[1], Annamaria Offidani[1]

[1]*Dermatological Clinic, Department of Clinical and Molecular Sciences, Polytechnic University of the Marche Region, Ancona, Italy.*

Abstract

Trichorhinophalangeal syndrome is an autosomal dominant disease caused by mutations in *TRPS* gene, characterized by skeletal, skin appendage, and endocrinological manifestations. Clinical presentation may vary widely, and the syndrome frequently remains undiagnosed. The diagnosis is mainly clinical, supported by radiographic images, and is confirmed by genetic investigation. Familiarity with this genetic disorder is crucial for providing correct and early identification, and for determining adequate supportive management, especially to prevent orthopedic complications.

Keywords: trichorhinophalangeal syndrome, hair disease, nail disease, genetic disorder

Received: 18 October 2021 | **Returned for modification:** 10 December 2021 | **Accepted:** 27 December 2021

Introduction

Trichorhinophalangeal syndrome (TRPS) is an autosomal dominant genetic disorder characterized by skeletal malformations, facial dysmorphism, and brittle hair. It is caused by a mutation of the *TRPS* gene located on chromosome 8q24, which codes for a transcription factor involved in the genesis and development of various organs. Several studies have demonstrated a correlation between genotype and phenotype, distinguishing three clinical variants: TRPS type I (Giedion syndrome), TRPS type II (Langer–Giedion syndrome, LGS), and TRPS type III, each with its own corresponding molecular profile. TRPS type I is caused by various kinds of alterations, including deletions, insertions, or translocations of chromosome 8 band q 24.1. TRPS type II is defined as a contiguous gene syndrome caused by a larger deletion, leading to the functional loss of the *TRPS1* gene at 8q23.3 and *EXT1* gene at 8q24.11. Finally, TRPS type III is characterized by missense mutations in the GATA DNA-binding zinc finger of the TRPS1 protein (1–3).

The effective prevalence of TRPS remains unknown, perhaps due to the widely variable manifestations of the disease, which often result in TRPS being underdiagnosed in many cases (2).

Case report

Our patient was a 17-year-old female, with fragile, sparse, thin hair with frontotemporoparietal hypotrichosis and sparse eyelashes and eyebrows, particularly in the middle-external third (Fig. 1). Her nails appeared fragile and thin. The patient reported a personal medical history of hip pain and fatigue during easy walking starting at age nine, supported by ultrasound relief of post-traumatic synovitis of the left hip associated with suspected femoral malformation. She presented a triangular face with a wide forehead, sunken eyes, and a pear-shaped bulbous nose with the tip pointing downward, associated with backward positioning of the nasal wings. The mouth had a thin upper lip and a long philtrum. The mandibular angle was more obtuse than the norm, associated with obvious prognathism (Fig. 2).

Skeletal abnormalities were noticed, including height at the 10th percentile, supernumerary teeth, brachydactyly of the hands and feet, and ulnar deviation of the interphalangeal joints (Fig. 3).

X-ray of the hips confirmed the presence of coarse structural anomalies affecting the femur, suggestive of aseptic femoral head necrosis. X-ray of the hands showed anomalies of the intermediate phalanx of the second ray and an osteostructural thickening of the ossification nucleus of the distal phalanges of the second and fifth fingers. Bone age was significantly delayed (Fig. 4).

Levels of thyroid hormones, cortisol, parathyroid hormone, growth factor, sexual hormones, prolactin, insulin-like growth factor 1 (IGF-1), and 25-hydroxyvitamin D3 were in the normal range.

Similar findings were equally evident in the face of the mother, with whom there was a fair resemblance (Fig. 5). Moreover, the mother also had a short stature and skeletal defects, including ulnar deviation of the toes and flat feet. She also reported that her hair grows very slowly.

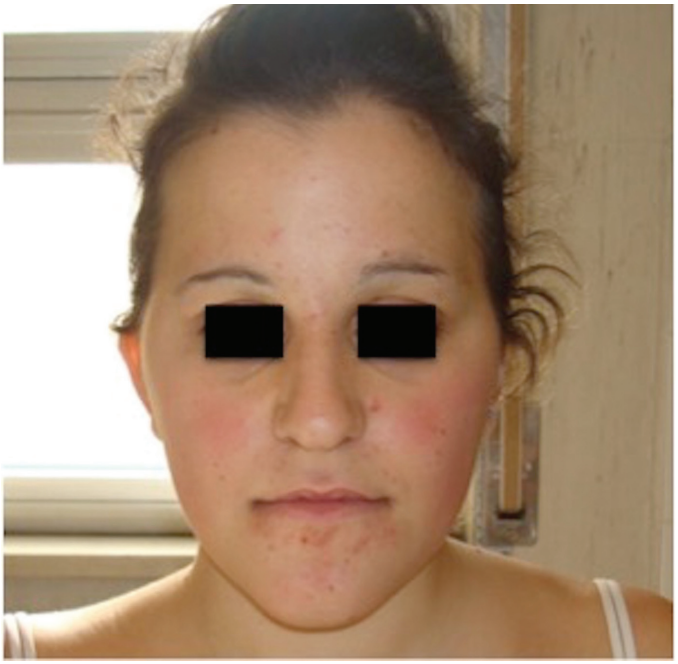

Figure 1 | Phenotypic cutaneous features: fine and sparse hair, hypotrichosis, and sparse eyelashes and eyebrows.

✉ Corresponding author: o.simonetti@univpm.it
*Oriana Simonetti and Giulia Radi contributed equally to the manuscript.

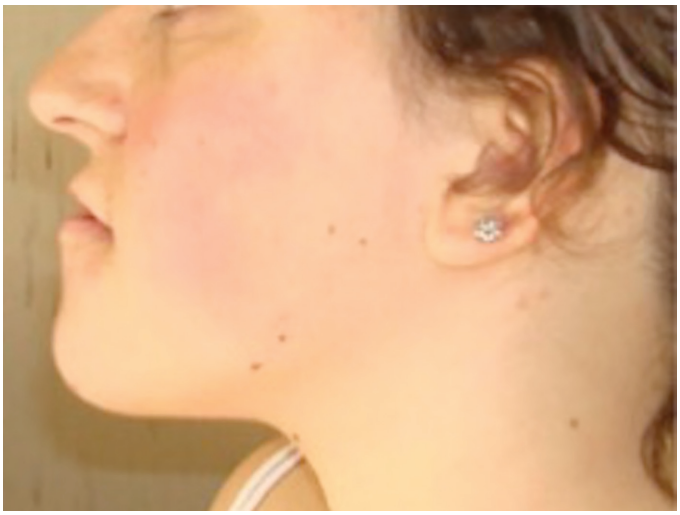

Figure 2 | Typical phenotypic features: bulbous nose, long philtrum, thin upper lip, and prominent forehead.

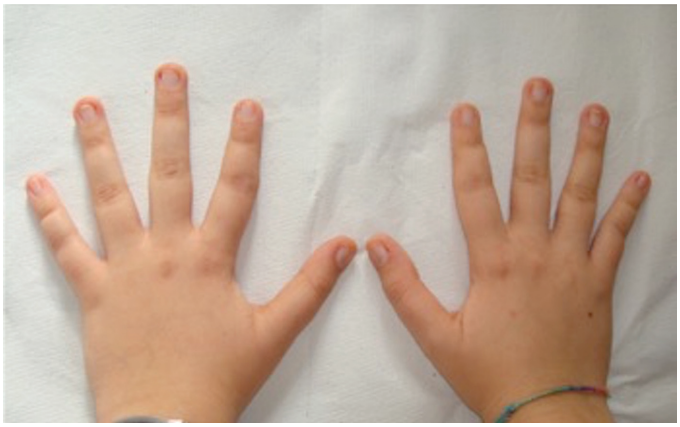

Figure 3 | Brachydactyly of the hands and ulnar deviation.

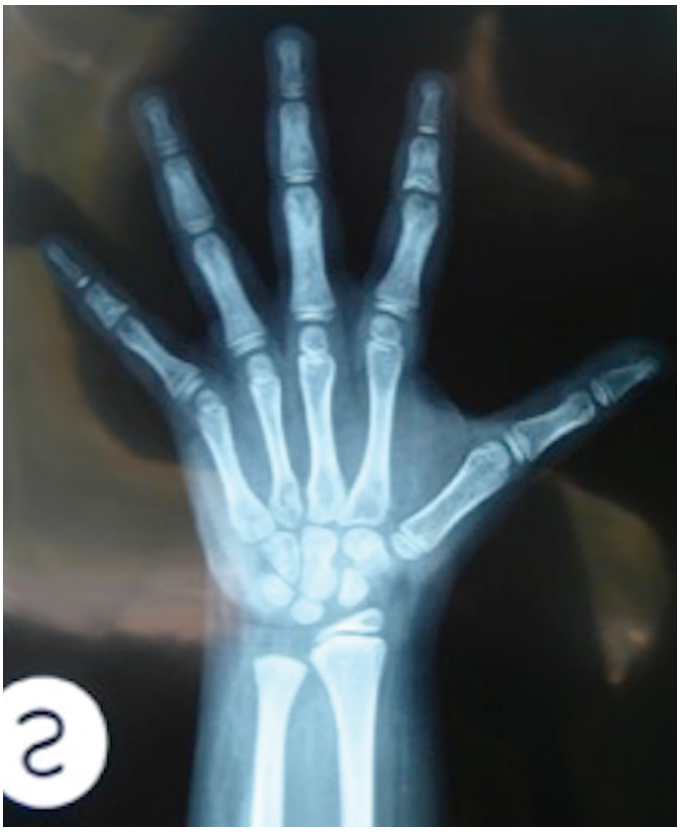

Figure 4 | Radiograph of the patient's left hand. Delayed bone maturation and cone-shape appearance of distal phalanges.

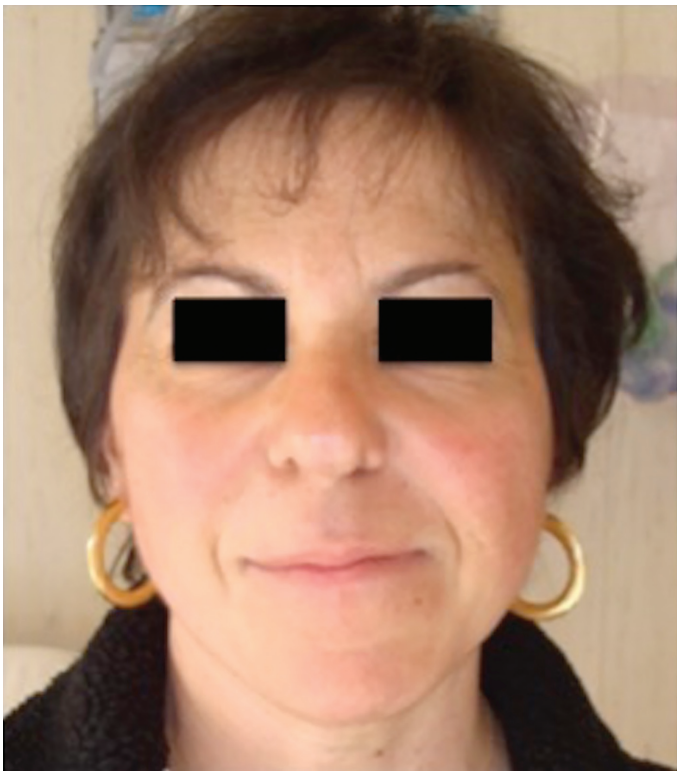

Figure 5 | The patient's mother: similar facial features.

Discussion

TRPS is characterized by wide clinical variability, and recent studies describe novel and recurrent alterations responsible for TRPS (4, 5). TRPS types I, II, and III share several phenotypical manifestations (3, 6, 7). Bony anomalies of the extremities are the most frequently observed, including brachydactyly and clinodactyly, short feet and metatarsals, and short metacarpal phalanges, followed by winged scapula, pectus carinatum, and scoliosis. More than 70% of patients present nonspecific hip malformations such as coxa vara, coxa plana, and coxa magna, and Perthes disease–like femoral head changes (8). In addition, patients may exhibit short stature. Moreover, patients present distinctive facial dysmorphism: a pear-shaped nose with a bulbous tip, hypoplastic nasal alae, low-set protruding ears, and a prominent malar eminence and orbital ridge. Distinctive signs are an elongated philtrum, thin upper vermillion border, and triangular face. Malocclusion, supernumerary teeth, microdontia, hypodontia, and micrognathia have been described (9). Dermatological features of interest concern the hair and nails. Some patients report slow nail growth so that they never need to cut them, with reduced length, an enlarged appearance, and a typical racket-like aspect. Leukonychia, koilonychia, onychodystrophy, and thin longitudinal striations are the most frequent alterations in TRPS cases. The best-known hair disorders are slow-growing, sparse, often poor-quality hair that breaks and tears easily (10, 11). Radiographic features usually confirm the clinical diagnosis of TRPS; the most important are cone-shaped epiphyses, mostly on the middle phalanges (12). The cone-shaped epiphyses result in mild metaphyseal convexity found from 2 years of age onward and lead to clinobrachydactyly at the time of ossification of the growth nuclei, which occurs prematurely in patients with TRPS. The same radiographic changes can occur in long bones, such as the femur, and result in hip malformation. Skeletal age is delayed relative to chronological age. TRPS

type I is the most common variant among trichorophalangeal syndromes, with more than 130 pathogenic variants described (7, 13). TRPS type II has a more severe clinical presentation of disease than type I, usually complicated by concomitant mild to severe mental retardation and multiple exostoses. In addition, joint laxity, skin laxity, microcephaly, sunken eyes, exotropia, tense and thickened nasal alae, and conductive hearing loss are described (14). Some authors consider TRPS type III to be a subclass of TRPS I aggravated by the presence of serious brachydactyly and significant short stature and growth retardation (3, 15). The great clinical variability of TRPS, in addition to the multiplicity of genetic alterations, also stems from the fact that the *TRPS* gene is expressed in various organs and causes anomalies in several apparatuses. Gai et al., using *TRPS1Δgt*- and *TRPS1*-deficient mice, suggested that *TRPS1* is particularly expressed in cartilage, kidneys, and hair follicles. In fact, *TRPS1* regulates the differentiation, proliferation, and apoptosis of chondrocytes through the interaction of several signaling molecules. In addition, *TRPS* is expressed in the kidney cells during nephron development, and *TRPS* haplo-insufficiency promotes renal fibrosis caused by unilateral ureteral obstruction by increasing Arkadia expression. In addition, the *TRPS1* gene widely influences hair follicle growth because it has been shown to be expressed at the level of dermal papillae and in mesenchymal cells surrounding hair pegs (16). Moreover, Fantauzzo et al. observed that *TRPS1* gene expression occurs in the hair follicle morphogenesis process in the nuclei of mesenchymal cells and in the nuclei of dermal papillae cells in human hair follicles during telogen and anagen (17). In *TRPS1* knockout animals, Michikami et al. showed a defect in the development of the mandibular condyle, which was smaller, whereas the glenoid fossa of the temporal bone was formed relatively normally. Therefore bones, joints, and hair follicles are the tissues that undergo the most evident anomalies as a consequence of the mutation of the *TRPS1* gene (18). In our case, the young patient showed typical skeletal anomalies of the bones of the face, femur, hands, and feet: facial dysmorphism with an obtuse jaw angle associated with prognathism, mild brachydactyly and clinodactyly, and short stature. The classic phenotype of TRPS type I was supported by the radiographic findings of cone-shaped epiphyses, mostly in the middle phalanges, and anomalies affecting the femur suggestive of aseptic femoral head necrosis. In a percentage ranging from 43 to 76%, a Legg–Perthes–Calvé–Waldenström–like syndrome affects the coxofemoral joint in patients with TPRS type I (8). No abnormalities of the kidneys and urinary tract were noticed. The involvement of the annexes was an aspect of dermatological relevance: sparse and fragile hair with slow growth, concomitant alopecia of the lateral third of the eyebrow, and thin longitudinal streaks of the nails completed the diagnosis. We decided to perform a genetic analysis, which showed heterozygous microdeletion of 8q24, sustaining the clinical diagnosis of TRPS type 1. In several cases published in the literature, a possible correlation of TRPS with metabolic alterations has been discussed. However, only sporadic associations with endocrinological disorders have been found: few cases of TRPS associated with hypoglycemia, diabetes and hypothyroidism have been described in the past (19, 20). More recently, some authors noticed growth hormone deficiency and bone density changes in patients with TRPS type I (21, 22). Growth hormone treatment has been shown to improve the outcome of growth and height in children with TRPS, even if more definitive results are needed (23). In our case, laboratory tests on the hormonal profile of thyroid hormones, cortisol, parathyroid hormone, growth factor, sex hormones, prolactin, IGF-1, and 25-hydroxyvitamin D3 were in the normal range. Finally, as regards the inheritance of the disease, it has been seen that it is transmitted as an autosomal dominant trait and has variable expression. The literature reports cases of multiple members of the same family affected by TRPS and other cases in which the mutation is sporadic. In familial forms, the syndrome is often diagnosed in a child that has a typical clinical presentation and the diagnosis is made backwards, even in one of the parents or older siblings (24, 25).

In our case, after a careful medical history and an objective examination of the parents, clinical characteristics such as short stature, clinobrachydactyly, and sparse hair that grows with difficulty made it possible to hypothesize a diagnosis of TRPS even in the mother, later confirmed by molecular analysis. TRPS also has a broad clinical spectrum due to various alterations that may occur on the gene. For this reason, it requires an orthopedic, dermatological, endocrinological, and genetic poly-specialist evaluation.

References

1. Momeni P, Glöckner G, Schmidt O, von Holtum D, Albrecht B, Gillessen-Kaesbach G, et al. Mutations in a new gene, encoding a zinc-finger protein, cause tricho-rhino-phalangeal syndrome type I. Nat Genet. 2000;24:71–4.
2. Lüdecke HJ, Schaper J, Meinecke P, Momeni P, Gross S, von Holtum D, et al. Genotypic and phenotypic spectrum in tricho-rhino-phalangeal syndrome types I and III. Am J Hum Genet. 2001;68:81–91.
3. Lüdecke HJ, Wagner MJ, Nardmann J, La Pillo B, Parrish JE, Willems PJ, et al. Molecular dissection of a contiguous gene syndrome: localization of the genes involved in the Langer–Giedion syndrome. Hum Mol Genet. 1995;4:31–6.
4. Hilton MJ, Sawyer JM, Gutiérrez L, Hogart A, Kung TC, Wells DE. Analysis of novel and recurrent mutations responsible for the tricho-rhino-phalangeal syndromes. J Hum Genet. 2002;47:103–6.
5. Chen LH, Ning CC, Chao SC. Mutations in TRPS1 gene in trichorhinophalangeal syndrome type I in Asian patients. Br J Dermatol. 2010;163:416–9.
6. Rodriguez-Serna M, Serrano G, Perez A, Aliaga. What syndrome is it? Trichorhinophalangeal syndrome. Pediatr Dermatol. 1993;10:385–7.
7. George S, Pulimood S, Korah I. Trichorhinophalangeal syndrome type I. J Eur Acad Dermatol Venereol. 1998;11:66–8.
8. De Barros GM, Kakehasi AM. Skeletal abnormalities of tricho-rhino-phalangeal syndrome type I. Rev Bras Reumatol Engl Ed. 2016;56:86–9.
9. Machuca G, Martínez F, Machuca C, Bullón P. Craniofacial and oral manifestations of trichorhinophalangeal syndrome type I (Giedion's syndrome): a case report. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1997;84:35–9.
10. Seitz CS, Lüdecke HJ, Wagner N, Bröcker EB, Hamm H. Trichorhinophalangeal syndrome type I: clinical and molecular characterization of 3 members of a family and 1 sporadic case. Arch Dermatol. 2001;137:1437–42.
11. Van Neste D, Dumortier M. Tricho-rhino-phalangeal syndrome: disturbed geometric relationships between hair matrix and dermal papilla in scalp hair bulbs. Dermatologica. 1982;165:16–23.
12. Giedion A. Phalangeal cone-shaped epiphyses of the hand: their natural history, diagnostic sensitivity, and specificity in cartilage hair hypoplasia and the trichorhinophalangeal syndromes I and II. Pediatr Radiol. 1998;28:751–8.
13. Maas SM, Shaw AC, Bikker H, Lüdecke HJ, van der Tuin K, Badura-Stronka M, et al. Phenotype and genotype in 103 patients with tricho-rhino-phalangeal syndrome. Eur J Med Genet. 2015;58:279–92.
14. Jones KL, Jones MC, del Campo M. Langer–Giedion syndrome. In: Jones KL, Jones MC, del Campo M, editors. Smith's recognizable patterns of human malformation. Philadelphia: Elsevier Saunders; 2013. p. 384–7.
15. Niikawa N, Kamei T. The Sugio–Kajii syndrome, proposed tricho-rhino-phalangeal syndrome type III. Am J Med Genet. 1986; 24:759–60.
16. Gai Z, Gui T, Muragaki Y. The function of TRPS1 in the development and differentiation of bone, kidney, and hair follicles. Histol Histopathol. 2011;26:915–21.
17. Fantauzzo KA, Bazzi H, Jahoda CA, Christiano AM. Dynamic expression of the zinc-finger transcription factor Trps1 during hair follicle morphogenesis and cycling. Gene Expr Patterns. 2008;8:51–7.

18. Michikami I, Fukushi T, Honma S, Yoshioka S, Itoh S, Muragaki Y, et al. Trps1 is necessary for normal temporomandibular joint development. Cell Tissue Res. 2012;348:131–40.
19. Parkhurst RD, Light GS, Bacon GE, Gall JC Jr. Tricho-rhino-phalangeal syndrome with hypoglycemia: case report with endocrine function studies. South Med J. 1972; 65:457–9.
20. Voigtländer V, Osswald F. The tricho-rhino-phalangeal syndrome. Dermatologica. 1978;156:34–9.
21. Sarafoglou K, Moassesfar S, Miller BS. Improved growth and bone mineral density in type I trichorhinophalangeal syndrome in response to growth hormone therapy. Clin Genet. 2010;78:591–3.
22. Stagi S, Bindi G, Galluzzi F, Lapi E, Salti R, Chiarelli F. Partial growth hormone deficiency and changed bone quality and mass in type I trichorhinophalangeal syndrome. Am J Med Genet A. 2008;146A:1598–604.
23. Merjaneh L, Parks JS, Muir AB, Fadoju D. A novel TRPS1 gene mutation causing trichorhinophalangeal syndrome with growth hormone responsive short stature: a case report and review of the literature. Int J Pediatr Endocrinol. 2014; 2014:16.
24. Foryś-Dworniczak E, Zajdel-Cwynar O, Kalina-Faska B, Małecka-Tendera E, Matusik P. Trichorhinophalangeal syndrome as a diagnostic and therapeutic challenge for paediatric endocrinologists. Pediatr Endocrinol Diabetes Metab. 2019; 25:41–7.
25. Nik Kantaputra P, Jotikasthira D, Carlson B, Wongmaneerung T, Quarto N, Khankasikum T, et al. TRPS1 mutation associated with trichorhinophalangeal syndrome type 1 with 15 supernumerary teeth, hypoplastic mandibular condyles with slender condylar necks and unique hair morphology. J Dermatol. 2020; 47:774–8.