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REVIEW

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Pathogenesis and potential therapeutic targets of trichorhinophalangeal syndrome; lessons obtained from animal studies

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Abstract

Trichorhinophalangeal syndrome (TRPS) is a rare genetic disease inherited in an autosomal dominant manner. It occurs in 1 in 100,000 people globally and is caused by several types of mutations of the TRPS1 gene. Since the first human patient was reported in 1966, typical and atypical pathologies, disease courses, and treatment case presentations have been reported. TRPS is characterized by sparse slow-growing fine hair, a bulbous nose with tented nares, and brachydactyly with cone-shaped epiphyses on the hands and feet. Growth retardation and hip dysplasia are also frequently observed, suggesting that hair and skeletal phenotypes are the major pathologies of TRPS. Several animal models have been established and studied intensively to address this rare disease. However, comprehensive treatment strategies for TRPS have not been established. In this review, we summarize TRPS pathologies and the characteristics of TRPS1 as an atypical GATA-type transcription factor. We review rodent strains that have contributed to our understanding of the in vivo roles of Trps1 and discuss their validity as animal models of TRPS. We also summarize diseases that demonstrate pathologies similar to TRPS and findings in their animal models.

KEYWORDS

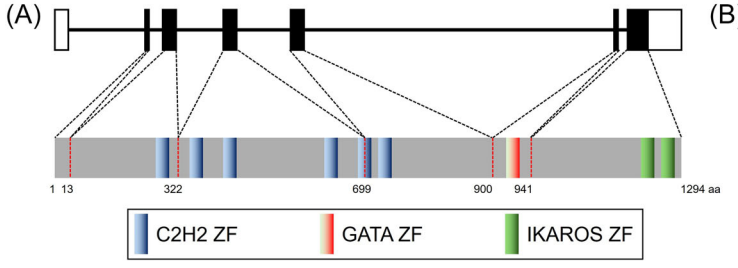
disease model, skeletal dysplasia, transcription factor, TRPS1

1 | TRPS HUMAN PATHOLOGIES

The first case report of a patient with trichorhinophalangeal syndrome (TRPS) was published by Giedion in 1966.[1] The report described patients with sparse fine hair (hypotrichosis), a bulbous nose with tented nares, cone-shaped epiphyses causing deformities in the phalangeal joint shape and digit alignment, and a short stature, which became prominent several years after birth. Autosomal-dominant inheritance has been established in most families with TRPS.[2] *TRPS1* has been identified as a disease-causing gene for TRPS,[3] and currently, TRPS is classified into the following three groups based on the type of *TRPS1* gene mutations: (1) TRPS I, characterized by deletions or nonsense mutations in the *TRPS1* gene; (2) TRPS II, characterized by deletion mutations in the *EXT1* and *RAD21* genes in addition to the deletion of the *TRPS1* gene; and (3) TRPS III, characterized by point mutations or missense mutations within the DNA-binding GATA-domain or transcriptional repressor Ikaros-type zinc finger (ZF) domain of the *TRPS1* gene[3–5] (Figure 1A,B). The cardinal triad features of all classes of patients are sparse, fine hair; a typical craniofacial appearance; and axial and appendicular skeletal deformities. Abnormalities in the hands and feet, especially epiphyseal coning, are common skeletal phenotypes in most cases. TRPS II (Langer-Giedion syndrome) presents similar pathologies to TRPS I and is characterized by additional features, including multiple exostoses (osteochondromas) formed around the scapulae, elbow, and knees. This type also exhibits mild-to-moderate intellectual disabilities.[6] TRPS III (Sugio-Kajii syndrome) is an extremely rare type with severe dysmorphic abnormalities of the hands and feet. Inflammation in the spinal column (osteochondritis) and scoliosis are relatively particular to TRPS III. We have summarized novel TRPS1 mutations reported after 2015,[7–19] as one of the largest-scale gene mutation summaries was published in 2015[5] (Figure 1B). The predicted protein structures of wild-type and R921Q mutant TRPS1, the causal mutation of TRPS III, show very little conformational differences (Figure 1C).

1.1 | Hair anomalies

TRPS is a congenital hair loss disease characterized by sparse, slow-growing scalp hair (congenital hypotrichosis) (Figure 2A). Hypotrichosis is observed in more than 90% of patients,[4,5] and is classified as genodermatosis



(B)

protein	type of mutation	reference
p.Asn13Lysfs*3	frameshift	Huang et al., 2022
p.Ser392*	nonsense	Herlin et al., 2024
p.Tyr446*	nonsense	Wang et al., 2020
p.Ser502Valfs*7	frameshift	Herlin et al., 2024
p.Leu664Cysfs*100	frameshift	Itoh et al., 2016
p.Ser747Tyrfs*6	frameshift	Herlin et al., 2024
p.Ser816Glufs*28	frameshift	Ozturk et al., 2023
p.Ser886*	nonsense	Wang et al., 2020
p.Cys909Ser	missense	Wang et al., 2020
p.Cys909Tyr	missense	Hufeland et al., 2015
p.Arg921Gln	missense	Fang et al., 2022
p.Tyr928Cys	missense	Karaca et al., 2019
p.Ala932Ser	missense	Smaili et al., 2017
p.His940Argfs*6	frameshift	Yagasaki et al. 2023
p.Asn952Argfs*2	frameshift	Ergoren et al., 2022
p.Ile1050Leu	missense	Herlin et al., 2024
p.Ser1067Argfs*3	frameshift	Gilman et al., 2017
p.Gly1073Phefs*2	frameshift	Herlin et al., 2024
p.Cys1233Tyr	missense	Levy-Shraga et al., 2020
p.His1246Arg	missense	Herlin et al., 2024

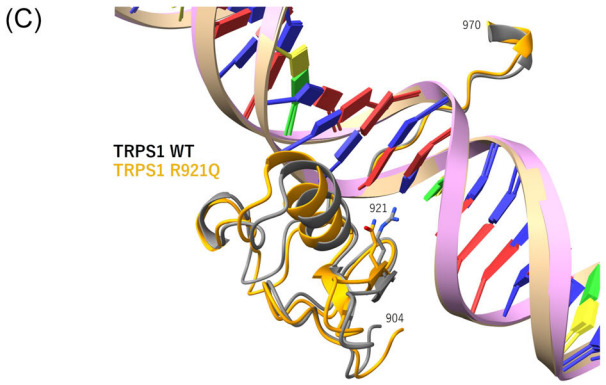


FIGURE 1 Protein structure of human TRPS1. (A) Illustration of genomic and protein structures of human TRPS1. The numbers below the protein structure indicate amino acid position. (B) List of TRPS1 mutations reported after 2015. (C) Structural models of the TRPS1-dsDNA complex predicted by AlphaFold3. The three-dimensional structures of the TRPS1 wildtype (gray) and the R921Q mutant (orange) were predicted as complexes with the dsDNA (AGATAA)x5/(TTATCT)x5. The dsDNAs from both models were superimposed for comparison. The residues 904–970 of TRPS1, which contain the GATA ZF motif, are shown together with the dsDNA. The side chains of the 921st residues of both TRPS1 models are also shown.

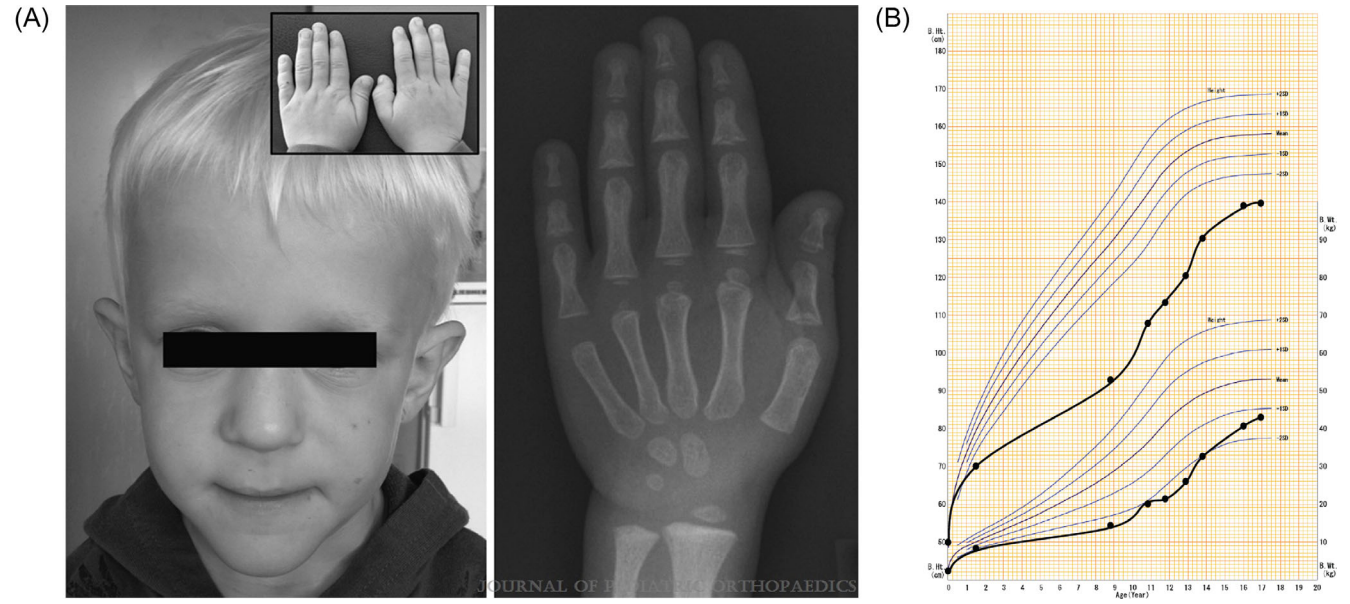


FIGURE 2 Appearance and growth curves of Trichorhinophalangeal syndrome patients. (A) Fine scalp hair, pear-shaped nose, long philtrum, and protruding ears are observed. The inset image shows the shortening of the digit length of the same patient. The right radiographic image of the left hand shows cone-shaped epiphyses of the middle phalanges of the second to fifth fingers. Adapted from "Trichorhinophalangeal Syndrome Type I: A Novel mutation and Perthes-like Changes of the Hip in a Family With 4 Cases Over 3 Generations" by Hufeland, Rahner, Krauspe from the Journal of Pediatric Orthopedics. By permission of Wolters Kluwer Health, Inc. (B) Growth curve of patient with Trichorhinophalangeal syndrome shows severe growth failure during childhood. Adapted from "A novel frameshift mutation in the TRPS1 gene caused Tricho-rhino-pahlangeal syndrome type I and III in a Japanese family" by Itoh, Kittaka, Niida, Saikawa from Clinical Pediatric Endocrinology. By permission of Clinical Pediatric Endocrinology.

with nonscarring hypotrichosis.[20] Hair alteration of diffuse alopecia with a broad forehead and partial alopecia of the lateral third of the eyebrow. In severe cases, patients present with nearly absent hair before they reach the 20th.[4,5] A biopsied specimen of the alopecia lesion displayed markedly reduced TRPS1 protein levels in the epidermis and the outer root sheath of the hair follicle.[21] Histologically, miniaturized hair follicles, sebaceous glands, and widely spaced cuticular scales are observed in the patients' hair.[22]

1.2 | Craniofacial and dental anomalies

A prominent feature of patients with TRPS is the characteristic facies.[23] Consistent facial characteristics include: (1) a bulbous, pear-shaped nose with tented and underdeveloped alae; (2) an elongated philtrum; (3) scant eyebrows in the lateral temporal portion; (4) large protruding ears; and (5) a thin upper lip (Figure 2A). Oral findings in patients with TRPS include anomalies in tooth number, delayed crown and root development with abnormal shapes, and extensive tooth decay due to hypomineralization.[4,5,23] A cephalometric study of patients with TRPS showed a shortened posterior face height, short mandibular body and ramus, superior deflection, and reduced size of the posterior cranial base.[24] Morphological analysis indicates that the typical facial appearance is primarily caused by dysplasia of the posterior cranial base. The cranial base is lengthened by endochondral ossification of the synchondroses: anterior spheno-ethmoidal (S-E) and posterior spheno-occipital (S-O) growth centers.[25] The S-E synchondrosis closes at approximately 6 years of age, while the S-O synchondrosis remains open until late in the second decade in humans.[26] As patients with TRPS display a high degree of shortening of the posterior portion of the face, defects in development or maintenance of the S-O synchondrosis may account for their skeletal abnormalities in the cranium. Due to developmental defects in the cranial bones, vision (40%) and hearing (10%) impairments are observed in some patients with TRPS.[4,5]

1.3 | Skeletal anomalies

TRPS is classified as a genetic skeletal dysplasia under "Group 19; Brachydactylies as part of syndromes."[27] The most characteristic radiologic abnormalities in TRPS involve the phalanges, which consist of an enlarged, irregular metaphyseal ending in the shape of a cone (cone-shaped epiphysis).[28] The patient's hands or feet

appear short and stubby, with clinodactyly of variable angulation[4] (Figure 2A). Growth failure, observed prenatally and becoming more prominent postnatally, is a common finding in TRPS patients[4,5] (Figure 2B). Clinically, delayed bone age during childhood and decelerated growth with adult short stature have been well described in patients with TRPS. However, the underlying pathological mechanisms remain unclear.

Hip joint anomalies are another common issue in TRPS[29,30] (Figure 3). Up to 50% of TRPS patients exhibit misalignment of the hip joint and hypermobility of the joints.[31] Over time, the joints tend to degenerate, leading to pain and a limited range of joint movement. The initiation of hip joint anomalies in TRPS resembles that in Perthes disease, which is a juvenile form of avascular osteonecrosis of the femoral head.[32,33] Although 30%–50% of patients with Perthes disease experience coxarthrosis symptoms,[34] the remaining patients undergo spontaneous regeneration of the femoral head.[35,36] In contrast, Perthes-disease-like hip changes in patients with TRPS later lead to severe deformities, severe pain, and progressive degenerative arthritis.[7,29,37]

1.4 | Other anomalies

Patients with TRPS have a wide range of pathologies, including cardiovascular and renal anomalies.[4,5] The congenital cardiac defects observed in patients with TRPS include non-ischemic dilated cardiomyopathy, mitral valve disease, atrial septal defects, and total anomalous venous return.[38–40] Some of the patients with TRPS are associated with bilateral renal hypoplasia leading to chronic renal failure.[41]

2 | TRPS1 IS AN ATYPICAL GATA-TYPE TRANSCRIPTION FACTOR

2.1 | TRPS1 is a multi-zinc finger-containing transcription factor

The human *TRPS1* gene is approximately 260.5 kb and located on chromosome 8q23.3. In mice, the *Trps1* gene spans 255.7 kb and is located on chromosome 15qC. TRPS1 is an evolutionarily well-conserved protein

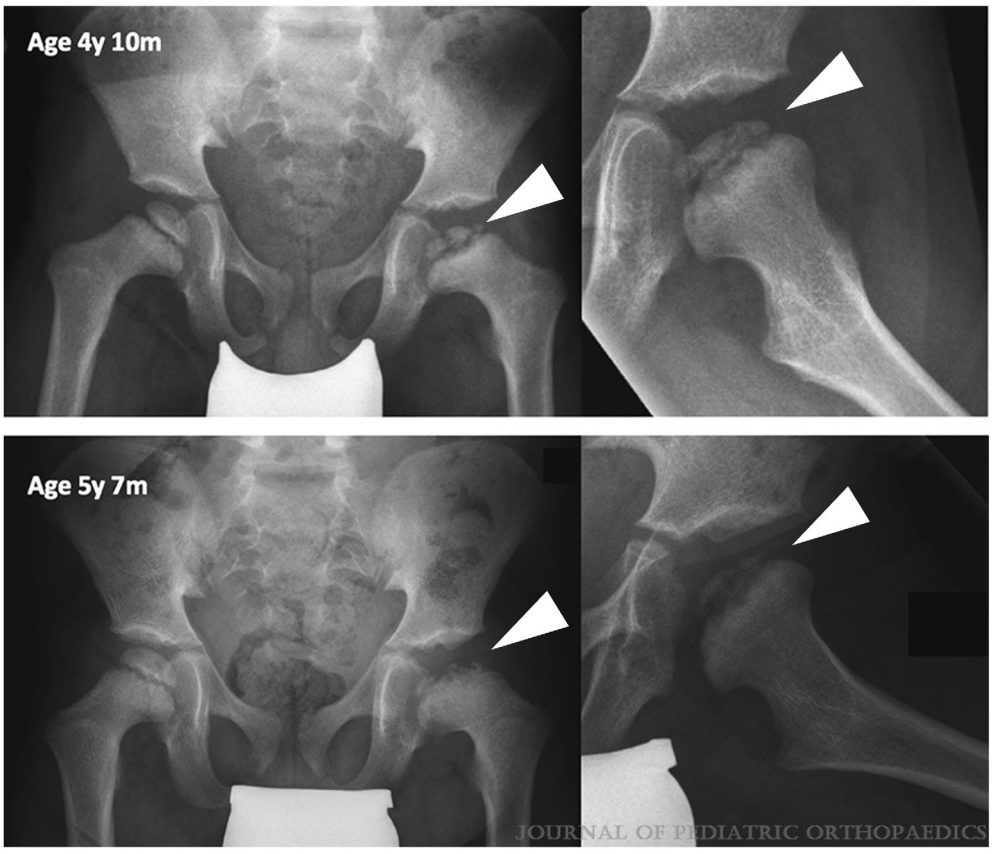


FIGURE 3 Pelvic radiographs of patients with Trichorhinophalangeal syndrome. Radiographs of the pelvis show bilateral coxa vara and Perthes-like changes (fragmented and flattened femoral heads) of the left hip (arrowhead). Adapted from "Trichorhinophalangeal Syndrome Type I: A Novel mutation and Perthes-like Changes of the Hip in a Family With 4 Cases Over 3 Generations" by Hufeland, Rahner, and Krauspe from the Journal of Pediatric Orthopedics. By permission of Wolters Kluwer Health, Inc.

characterized by the presence of nine ZF motifs.[42] The types of zinc finger motifs consist of six classical C_2H_2-ZF, two Ikaros C_2H_2-ZF, and one GATA C_4-ZF sequences (Figure 1A).[43–46] The GATA-type ZF motif is considered a DNA-binding site (thus, required for its transcriptional activity), and a closely located nuclear localization signal has also been identified.[47] TRPS1 belongs to the family of GATA transcription factors, all of which are intimately involved in organ and tissue development.[42,48] As TRPS1 contains only one GATA-ZF motif, whereas all other GATA family transcription factors contain two, TRPS1 is categorized as an "atypical" GATA transcription factor.[42] TRPS1 is expressed in a wide range of tissues and is involved in bone, kidney, and hair development.[49]

2.2 | Transcriptional activities of TRPS1

The transcriptional actions of TRPS1 seem to be context-dependent and have not been comprehensively studied, especially during developmental stages. TRPS1 is primarily defined as a transcriptional repressor because of its Ikaros-ZF domain, which shows strong transcriptional repression activity in a biochemical assay.[42] The Pro-X-Asp-Leu-Ala contact motif is associated with the C-terminal binding protein co-repressor complex.[46] Ikaros ZF factors have been shown to regulate gene expression in several ways, including (1) by association with chromatin remodeling complexes, such as nucleosome remodeling deacetylase (NuRD), (2) by promoting the activity of RNA polymerase II, and (3) by inducing chromosomal conformation changes.[50,51] As expected, global gene expression analysis revealed that several extracellular matrix molecules and hair follicle stem cell maintenance factors are upregulated in *Trps1*-knockout vibrissae follicles.[52,53] However, a number of downregulated genes were concomitantly identified in the same assay.[52] Potential direct target genes of Trps1 include *Lhx2*, *Sox18*, and *Sox21*. *Lhx2*-knockout mice display a 40% reduction in pelagic follicle density.[54] Point mutations in *Sox18* have been shown to underlie the raged (Ra) mouse phenotype, which is characterized by varying degrees of coat sparseness.[55] *Sox21*-KO mice exhibit cyclic alopecia beginning in the early postnatal period.[56]

Of note, the loss of *Trps1* results in significant upregulation of *Sox9* in the vibrissa follicle, as Trps1 directly binds to the *Sox9* promoter to repress its expression.[53] *Sox9* is a master gene involved in hair follicle development and is required for the specification of hair follicle stem cells.[57,58] The importance of Sox9 in hair follicle development is also evidenced by *Shh*- or *Gli2*-KO mouse embryos, which show markedly reduced hair follicle formation concomitant with reduced *Sox9* expression levels.[57] The upregulation of *Sox9* caused by the loss of *Trps1* may disturb progenitor cell specification or maintenance (Figure 4A).

Loss of *Trps1* reduces the proliferation rate of long bone growth plate chondrocytes. The distal region of the long bone cartilage anlage (Figure 4B) marked by *PTHrP* expression is significantly reduced in length.[59] A reduced distal region in $Trps1^{\Delta gt/\Delta gt}$ mice (one of the Trps1 mutant strains which will be described in chapter 3) has also been observed in *Gli3*-mutant mice ($Gli3^{Xt\text{-}J}$ mice).[59–62] Gli3 is one of the signal transducers of the Hedgehog pathways, and the genetic interactions between *Gli3* and *Trps1* have been intimately studied. Gli3 represses the transition from distal to columnar chondrocytes, while the switch from proliferating to hypertrophic chondrocytes is regulated by the Gli3-dependent expression of *PTHrP*.[62] When *Gli3* is deleted in $Trps1^{\Delta gt/\Delta gt}$ mice, the reduced distal zone is similar to that in $Trps1^{\Delta gt/\Delta gt}$ or $Gli3^{Xt\text{-}J/Xt\text{-}J}$ mice which suggests that Trps1 and Gli3 cooperate to maintain the distal zone via similar mechanisms.[59] Reduced chondrocyte proliferation is not observed in $Gli3^{Xt\text{-}J/Xt\text{-}J}$ mice, whereas $Trps1^{\Delta gt/\Delta gt}$ mice exhibit a significant reduction in chondrocyte proliferation.[59,63] $Trps1^{\Delta gt/\Delta gt}$;$Gli3^{Xt\text{-}J/Xt\text{-}J}$ mice display reduced proliferation, but activating Hedgehog signaling in the chondrocytes of $Trps1^{\Delta gt/\Delta gt}$ mice shows an increased proliferation rate compared to $Trps1^{\Delta gt/\Delta gt}$ mice, suggesting that the differentiation of columnar and hypertrophic chondrocytes is supported by Trps1, independent of Gli3.[59] Importantly, Trps1 physically interacts with the activator form of Gli3 (Gli3A).[59] Formation of the Gli3a-Trps1 complex results in the inhibition of Gli3A activity; thus, Trps1 acts like Gli3R to antagonize Gli3A function and maintains the distal zone.

During chondrocyte maturation, Gli3A and Trps1 bind to Wnt5a regulatory regions, and increase *Wnt5a* expression levels to induce chondrocyte hypertrophy.[64] Reduced *Wnt5a* expression levels in mice result in skeletal phenotypes that resemble those of *Trps1* and *Gli3* mutants.[59,62,65] Thus, *Wnt5a* may be a downstream target of Trps1 during endochondral ossification, and the interaction between Trps1 and Ihh/Gli3 signaling seems to be indispensable for normal endochondral ossification (Figure 4B).

Wnt5a signals by binding to a membrane protein complex consisting of Frizzled, Ror2, Vangl2, and Ryk, which initiates planar cell-polarizing (PCP) functions via non-canonical Wnt signal activation (Figure 4C).[66–70] WNT molecules bind to frizzled receptors, which are associated with ROR2. This ligand binding triggers the association of Vangl2 and Ryk into the complex, which phosphorylates and stabilizes the Vangl2 protein, resulting in the enhancement of the receptor complex

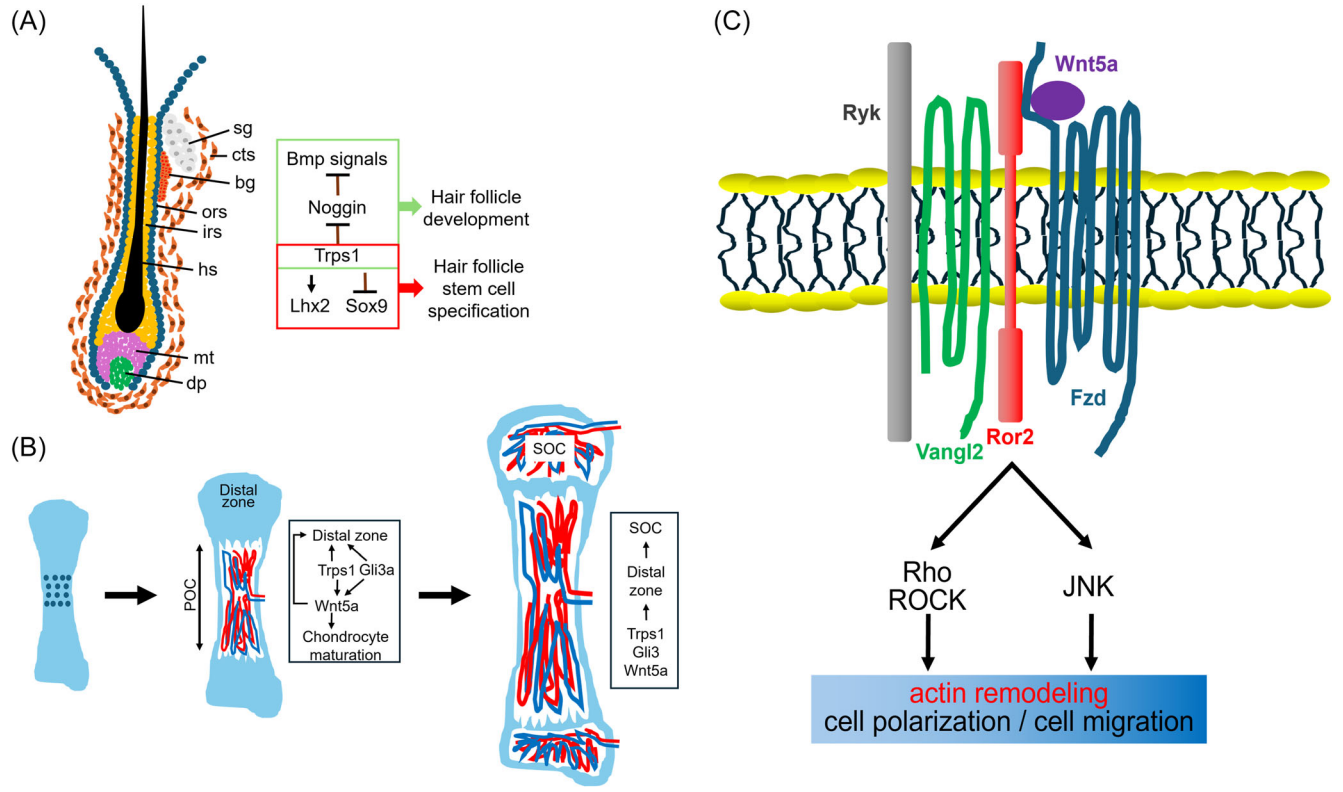


FIGURE 4 Schematic illustration of mature hair follicle (A), developmental course of endochondral bones (B), and signaling axis of the non-canonical WNT pathways. (A) Longitudinal image of the mature hair follicle and signal cascades regulated by Trps1 for hair follicle development or stem cell specification. (B) Scheme of long bone development from cartilage template formation toward primary and secondary ossification center formation. Signal cascades regulated by Trps1 for maintenance of distal epiphyseal zone of the cartilage anlage and further secondary ossification center formation. (C) Non-canonical WNT signaling pathways activated by Wnt5a binding to the receptor complex consisting of Fzd, Ror2, Ryk, and Vangl2. The ligand binding activates the intracellular processes of actin remodeling, finally leading to planar cell polarity movements of the multi-cell sheet. *Key*; bg: Bulge, cts: Connective (fibrous) tissue sheath, dp: Dermal papilla, Fzd: Frizzled, hs: Hair shaft, irs: Inner root sheath, mt: Matrix tissue, ors: Outer root sheath, POC: Primary ossification center, Ror2: Receptor tyrosine kinase-like orphan receptor 2, Ryk: Receptor-like tyrosine kinase, sg: Sebaceous gland, SOC: Secondary ossification center, Vangl2: Vangl planar cell polarity protein 2.

association.[70,71] WNT molecules bind to the receptor complex and regulate PCP pathways, which lead to the coordinated alignment of cells within the plane perpendicular to the cellular apico-basal axis.[66,67]

In murine models, *Wnt5a*, *Ror2*, and *Vangl2* mutants bear many similar disease phenotypes and display shortened limbs along the P-D axis.[65,70,72–75] Although the *Wnt5a*-KO phenotype is more severe than the phenotypes of *Ror2*-KO or *Vangl2*-KO mice, $Ror2^{-/-}$;$Vangl2^{-/-}$ double-KO mice show almost identical phenotypes to *Wnt5a*-KO mice.[70] Ryk is a Wnt5a-binding protein that interacts with Vangl2 both genetically and biochemically.[71] *Ryk*-KO mice do not display an obvious PCP phenotype,[68] but $Ryk^{-/-}$; $Vangl2^{-/-}$ double KO embryos exhibit a more severe phenotype than *Vangl2*-KO mice and show a shortened A-P body axis and limb, similar to *Wnt5a*-KO mice.[71]

TRPS1 is implicated in human cancers including prostate cancer,[45,76] leukemia,[77] colon cancer,[78] endometrial cancer,[79] and breast cancer.[80,81] Especially, TRPS1 is proposed as a novel breast cancer marker, expressed in 75% in the breast cancer cohort, making it a useful diagnostic tool.[82,83] TRPS1 amplifications are frequently observed in breast cancers with poor survival.[84,85] TRPS1 and CHD4/NuRD complex (CHD; chromodomain helicase DNA-binding protein) form precision-guided transcriptional repression machinery in which TRPS1 guides the machinery to specific target sites by recognizing GATA elements, and thereafter CHD4/NuRD represses the transcription of target genes[86] (Figure 5A).

TRPS1 was recently identified as a potent repressor of YAP-dependent transcriptional activation.[87] Yes-associated protein (YAP), the downstream transducer of the Hippo pathway, is a key regulator of organ size, differentiation, and tumorigenesis.[87,88] TRPS1 globally regulates YAP-dependent transcription by binding to a large set of genomic sites, mainly at enhancer regions

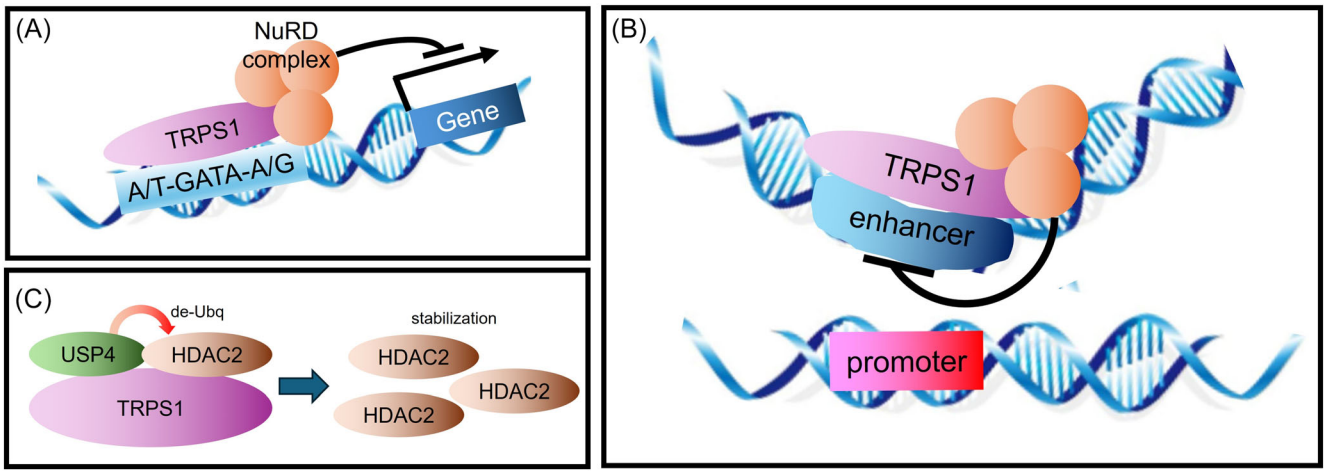


FIGURE 5 Modes of action of TRPS1 as a transcriptional repressor. (A) TRPS1 binds to the A/TGATAA/G sequence located near the promoter sites and recruits the NuRD repressor complex to repress gene transcription. (B) TRPS1 binds to the A/TGATAA/G sequence located at the enhancer sites and recruits the NuRD repressor complex to deacetylate the nucleosome located at the enhancer sites, leading to inhibition of enhancer and promoter interaction. (C) TRPS1 strengthens the interaction of de-ubiquitinase, USP4, and deacetylase, HDAC2, thereby stabilizing HDAC2 protein. HDAC2 thereafter deacetylates the nucleosome, resulting in transcriptional repression.

(Figure 5B). Thus, TRPS1 can function as a transcriptional repressor by recruiting repressor complexes to either promoter or enhancer regions.

Another mode of the action of TRPS1 is through functioning as a scaffold protein. TRPS1 recruits and enhances the interaction between Ubiquitin-specific peptidase 4 (USP4) and Histone deacetylase 2 (HDAC2), leading to HDAC2 de-ubiquitination.[89,90] Stabilized HDAC2 implements the transcriptional repression program by deacetylating H4K16ac (Figure 5C). The understanding of how TRPS1 represses specific gene transcription has been relatively well studied; on the other hand, how TRPS1 could act as an activator is still undefined.

3 | ANIMAL MODELS OF TRPS

Various TRPS model mice have been reported. They have contributed to a deeper understanding of the etiology of disease onset and progression, unveiling gene regulatory mechanisms, and identifying potential therapeutic targets. In this section, we summarize hair, craniofacial, and skeletal anomalies, which are the cardinal pathologies observed in human TRPS and in mouse models of TRPS (Table 1).

3.1 | *Trps1*$^{\Delta gt}$ mice

The first genetically engineered *Trps1* mutant was reported in 2002.[91] This strain lacks amino acids 888–928 of mouse Trps1, which includes the GATA-type zinc finger motif, but retains the nuclear localization sequence located just adjacent to its C-terminus (Figure 6). The *Trps1*$^{\Delta gt}$ strain is an in-frame deletion of the GATA ZF domain and is assumed to be a specific murine model of human TRPSI.[4]

3.1.1 | Hair follicle phenotypes

Intriguingly, there is a mild defect in pelage hair development in the *Trps1*$^{\Delta gt/+}$ strain; however, a detailed analysis has only been performed in homozygous *Trps1*$^{\Delta gt/\Delta gt}$ mice.[52,53] The potential transcriptional targets of Trps1 have been identified through *Trps1*$^{\Delta gt/\Delta gt}$ mice analysis, which is described in chapter 2.2.

3.1.2 | Craniofacial and long bone phenotypes

Trps1$^{\Delta gt/+}$ mice show facial anomalies, including mild micrognathia and a narrow-arched palate, although no cleft palate is observed. Reduced bone density has also been observed in female *Trps1*$^{\Delta gt/+}$ mice, and *Trps1*$^{\Delta gt/+}$ mice show a high incidence of thoracic kyphoscoliosis at the age of 3 months. Maas et al. reported that 30% of patients with TRPS show scoliosis in the trunk region.[5] *Trps1* has been identified as one of the bone mineral density (BMD) quantitative trait loci.[92,93] In humans, genome-wide association studies have demonstrated that a single nucleotide polymorphism (rs4355801) mapped to the same chromosomal locus as *TRPS1*

TABLE 1 Summary of the pathological phenotypes observed in animal disease models related to Trichorhinophalangeal syndrome.

Mouse strain	*Trps1* expression	Hair phenotypes	Craniofacial phenotypes	Other skeletal phenotypes	Other remarkable phenotypes	References
Trps1$^{\Delta gt}$ mice	Expresses inframe GATA-ZF deleted Trps1 protein	Vibrissae follicles absent and reduced hair follicles	Cleft palate in homozygous Narrow palate in heterozygous	Accelerated perichondrium ossification Abnormal epiphyseal growth plate structure Reduced bone density	*Trps1*$^{\Delta gt/\Delta gt}$ homozygous Mice are neonatally lethal	Malik et al.[42] Napielala et al. (2008) Wellings et al. (2009, 2020)
Trps1-KO mice	No expression	Vibrissae follicle severely reduced and minituarized hair follicles	Micrognathia Infrequent cleft palate	Abnormal epiphyseal growth plate structure	*Trps1*-KO are neonatally lethal Abnormal kidney development	Suemoto et al.[100] Gai et al. (2009, 2010) Michikami et al.[103]
Trps1-Flox mice (*Col1a1*CreER; *Trps1*$^{Flox/Flox}$)	Conditional deletion in osteoblasts/ odontoblasts/ cementoblasts	Not determined	Hypomineralized tooth hard tissue Impaired cementogenesis	Not determined	Not determined	Socorro et al.[107] Fujikawa et al.[109]
Trps1$^{\Delta int}$ mice	Reduced *Trps1* expression in several organs/cells	Not determined	Mild micrognathia	Growth retardation Acetabular dysplasia Patella dislocation Delayed SOC formation	Not determined	Saeki et al.[110]

Note: The brief findings of each animal disease model and their major reference documents are listed.

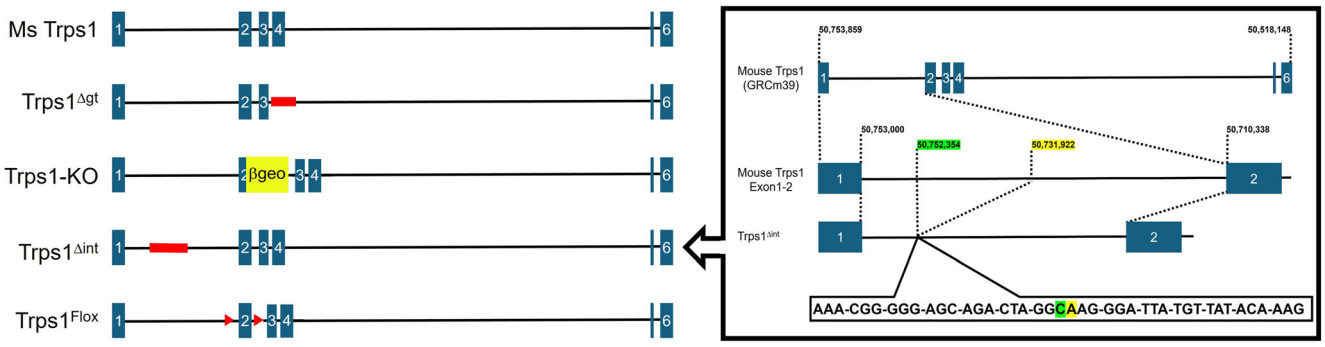


FIGURE 6 Genomic structures of TRPS animal models. The genomic structures of Trps1 mutant mouse strains. Trps1$^{\Delta gt}$ allele lacks exon 4, resulting in the production of Trps1 protein lacking the GATA ZF motif. Trps1-KO allele contains in-frame *β*geo cDNA sequence within the exon containing the translation start codon. Trps1$^{\Delta int}$ allele lacks approximately 20 kb of the first intron of the Trps1 gene. Trps1^{Flox} allele has two LoxP sequences inserted flanking exon 2.

(8q24.12) is significantly associated with osteoporosis.[30,94] Importantly, a significant reduction in bone mass has been recently described as a new feature of human TRPS I.[95,96] Thus, the reduced BMD observed in *Trps1*$^{\Delta gt/+}$ mice is consistent with the pathology observed in human TRPS.

Trps1$^{\Delta gt/\Delta gt}$ mice have a 100% penetrant cleft palate.[97] A narrow palate is observed in 70% of patients with

TRPS,[5] and a cleft palate is an uncommon observation but has been reported to occur in some patients.[98]

Long bone development occurs via endochondral ossification.[99] Mesenchymal cells undergo chondrocyte differentiation to form cartilage templates for future use as skeletal templates. The middle portion of the cartilaginous template ceases to proliferate and enlarges to differentiate into hypertrophic chondrocytes. The hypertrophic chondrocyte layer is replaced by invading osteoblast progenitors to form the primary ossification center in association with vascular and osteoclast invasion (Figure 4B). The fibrous perichondrium surrounding the cartilage template directly differentiates into bone-forming osteoblasts and forms the periosteum. Therefore, chondrogenesis and osteogenesis proceed cooperatively through complex interactions during endochondral ossification.

Trps1$^{\Delta gt/\Delta gt}$ mice show long bone development anomalies.[63] In the growth plates of *Trps1*$^{\Delta gt/\Delta gt}$ mice, delayed chondrocyte differentiation and accelerated mineralization of the perichondrium have been observed.[63] *Runx2* and *Patched 1* (*Ptch1*) expression levels are increased in the perichondrium of *Trps1*$^{\Delta gt/\Delta gt}$ mice, suggesting increased Hedgehog signaling in these cells. Trps1 physically associates with Runx2 and represses Runx2-mediated transcription in vitro.[63] Importantly, the expanded perichondrial mineralization domain observed in *Trps1*$^{\Delta gt/+}$ mice is reduced to wild-type levels in *Trps1*$^{\Delta gt/+}$;*Runx2*$^{+/-}$ heterozygous mice, indicating the presence of genetic interactions between Trps1 and Runx2 during long bone development.[63]

3.2 | *Trps1*-KO/*βgeo* (*Trps1*-KO) mice

The second *Trps1* mutant strain was generated by in-frame replacement of the *Trps1* exon containing the initiation codon with the beta-Geo (a fusion gene of beta-galactosidase and neomycin) sequence (*Trps1*-KO mice; Figure 6).[100] Heterozygous *Trps1*-KO mice have not been analyzed in detail; however, homozygous *Trps1*-KO mice show an early postnatally lethal phenotype, as observed in *Trps1*$^{\Delta gt/\Delta gt}$ mice.[100] This strain is used as a mouse model of human TRPSI.

3.2.1 | Hair follicle phenotypes

The number of vibrissa follicles is reduced in *Trps1*-KO mice,[100] and the number of hair follicles is reduced by half in *Trps1*-KO mouse skin (Figure 7).[103] Noggin expression levels are significantly reduced in *Trps1*-KO mouse skin, and consequently, Bmp signaling is upregulated. Exogenous Noggin treatment rescues the number of hair follicles in *Trps1*-KO mouse tissues.[101]

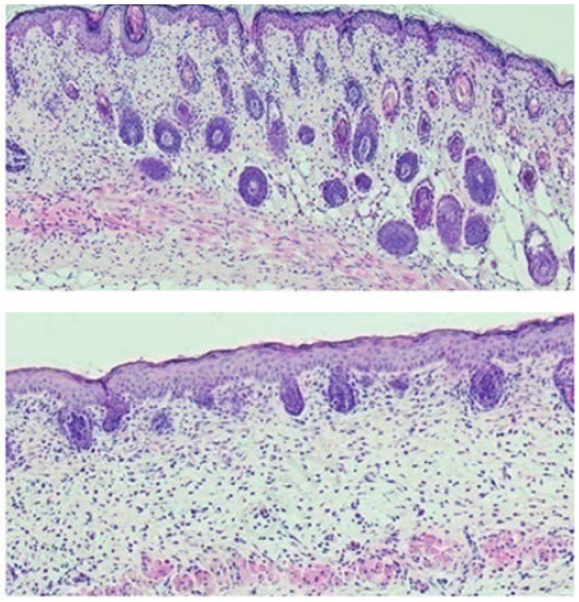


FIGURE 7 Histological sections of dorsal skin of wild-type (WT) and Trps1-KO (KO) mice. HE-stained sections of the dorsal skin of newborn pups. Trps1-KO section shows a reduced number of hair follicles. Adapted from "Trps1-deficient transplanted skin gave rise to a substantial amount of hair: Trps1 is unnecessary for hair development" by Zhang, Nakamura, Furukawa, Muragaki from Dermatology Reports.

Surprisingly, transplantation of *Trps1*-KO newborn mouse skin into the back of immunocompromised nude mice results in substantial hair formation,[102] although the hair is thin and soft.

3.2.2 | Craniofacial and long bone phenotypes

Craniofacial phenotypes have also been studied in *Trps1*-KO mice. Suemoto et al. demonstrated that the snout length of *Trps1*-KO mice is shorter than that of control mice.[100] Furthermore, the KO mice display micrognathia, mainly affecting the proximal region of the developing lower jaw. Indeed, the morphogenesis of most components of the temporomandibular joint appears abnormal. Joint disks and cavities are not formed.[103] Furthermore, the condylar growth plate loses its integrity and ability to expand.[104] Although *Trps1*$^{\Delta gt/\Delta gt}$ mice show a fully penetrant cleft palate, *Trps1*-KO mice only occasionally exhibit a cleft palate (N.S. and M.A., unpublished).

In the long bone growth plate, *Trps1* is dynamically expressed predominantly in articular and prehypertrophic chondrocytes.[105] The growth plates of *Trps1*-KO mice show a markedly elongated proliferation zone, although both the proliferation and apoptosis rates are

reduced.[100] In *Trps1*-KO chondrocytes, Stat3 protein levels and activity are increased.[100] Trps1 represses Stat3, which, in turn, controls chondrocyte proliferation and survival. *Trps1* deficiency enlarges the proliferation zone of the growth plate and upregulates PTHrP (expressed in the distal chondrocyte zone (Figure 4B)) levels, potentially affecting the Indian hedgehog (Ihh)/PTHrP feedback loop in the long bones of *Trps1*-KO mice.[106] The causes of the discrepancy between the reduced ($Trps1^{\Delta gt/\Delta gt}$) and expanded (*Trps1*-KO) distal chondrocyte zones between the two different *Trps1*-mutant mice are currently unknown, but it should be mentioned that the $Trps1^{\Delta gt}$ protein is expressed in $Trps1^{\Delta gt/\Delta gt}$ mice, while the Trps1 protein itself is not expressed in *Trps1*-KO mice. $Trps1^{\Delta gt}$ may affect signaling pathways, including Gli-mediated pathways, as the C_2H_2-type ZF motif is still present in the $Trps1^{\Delta gt}$ protein, which can interact with Gli3A.[59]

3.3 | *Trps1*-Flox mice

Because both $Trps1^{\Delta gt/\Delta gt}$ and *Trps*-KO mice showed early postnatal lethal phenotypes, a conditional *Trps1*-KO strain was established (Figure 6).[107] When *Trps1* was conditionally knocked out in osteoblasts and odontoblasts (using 2.3 kb *Col1a1*CreERT2), mineralization defects were observed in both tooth enamel and dentin.[107] Severe tooth root exposure was observed in conditional *Trps1*-KO mice, indicating impaired alveolar bone formation. Impaired dentin mineralization with a large dental pulp space has been reported in patients with TRPS.[108] Furthermore, considerable delays in root and crown development, malocclusion with abnormal tooth shape, and extensive caries (tooth decay) have been reported in patients with TRPS.[23] Teeth of conditional *Trps1*-KO mice were indeed more prone to acid-induced demineralization. Recently, defects in cementogenesis and tooth root formation have also been reported in the same conditional KO strain.[109]

3.4 | $Trps1^{\Delta Enh}$ mice

Since the postnatal skeletal phenotypes of TRPS cannot be investigated using conventional KO animal models, distinct strategies need to be established. To this end, we investigated the gene-regulatory enhancer region(s) of mouse *Trps1*.[110] Based on assays for transposase-accessible chromatin sequencing to identify open chromatin regions and chromatin immunoprecipitation sequencing to unveil transcriptionally active histone modifications using primary murine chondrocytes, several candidate regions for *Trps1* regulatory elements in the mouse genome have been identified. Genome editing strategies have been applied to delete these regions, either individually or simultaneously, to generate enhancer-KO mouse lines.[110] In this section, we focus on describing the phenotypes of $Trps1^{\Delta int}$ mice (Figure 6), as other generated mice only show subtle phenotypes, even when one allele of the *Trps1* gene was simultaneously deleted.[110] In $Trps1^{\Delta int}$ mice, the region within the first intron of *Trps1* (GRCm39; 50,731,923–50,752,354) is deleted without modification of any of the *Trps1* exon sequences (Figure 6). The deleted sequence contains two enhancer candidate regions, 3 and 5 kb in length. In $Trps1^{\Delta int}$ mice, these two regions are simultaneously deleted by two guide RNAs, resulting in a 20 kb deletion within the first intron. Reduced *Trps1* gene expression levels have been confirmed in various organs of $Trps1^{\Delta int}$ mice.[110] As hair follicle phenotypes have not been studied in this strain, we summarize the skeletal phenotypes observed in $Trps1^{\Delta int/\Delta int}$ mice in the following section.

3.4.1 | Craniofacial and long bone phenotypes

The craniofacial phenotypes are subtle in $Trps1^{\Delta int/\Delta int}$ mice. They show only a slight miniaturization of the mandibular condyle at birth.[110] Axial and appendicular skeletons of $Trps1^{\Delta int/\Delta int}$ mice showed normal morphology at birth. However, this mutant displayed significant growth defects starting at approximately the second week after birth. The severity of the growth defects became more obvious when one allele of *Trps1* was deleted simultaneously ($Trps1^{\Delta int/-}$ mice).[110] Given that growth retardation is a prominent feature of TRPS (especially in TRPS III),[4,5] $Trps1^{\Delta int/\Delta int}$ mice can serve as a model of TRPS that recapitulates postnatal pathologies. There were fewer mice of the $Trps1^{\Delta int/-}$ genotype than expected at weaning, indicating that most $Trps1^{\Delta int/-}$ mice died perinatally, as the proportion of mice retrieved for each genotype was as expected during the embryonic period.[4,5] Furthermore, the surviving $Trps1^{\Delta int/-}$ mice did not give birth to pups. All these observations suggest that there may be a threshold of *Trps1* expression for normal growth, survival, and also fertility.

$Trps1^{\Delta int}$ mice exhibited several other skeletal abnormalities, namely, (1) acetabular dysplasia, (2) patellar dislocation (only detected in $Trps1^{\Delta int/-}$ mice), and (3) delayed secondary ossification center (SOC) formation in the long bone epiphysis (Saeki et al., 2024).[110] Hip joint abnormalities are frequently observed in patients with TRPS, and the importance of a thorough clinical investigation of hip changes in children with TRPS has

been emphasized, as hip joint abnormalities may lead to severe hip diseases.[111,112] *Trps1*$^{\Delta int/\Delta int}$ mice show immature and shallow acetabular formation, resulting in undercoverage of the femoral head.[110]

An abnormally flat trochlear groove has been observed in the distal femur of *Trps1*$^{\Delta int/-}$ mice.[110] This dysplasia results in bilateral medial patellar dislocation in *Trps1*$^{\Delta int/-}$ mice. Repeated patellar dislocation has been reported in patients with TRPS.[113] Dislocation of the patellofemoral joint often leads to cartilage fractures and ligament ruptures.[114,115] Trochlear dysplasia is present in most patients suffering from patella dislocation (>90%), and recurrent patellar dislocation is a well-known risk factor for knee osteoarthritis.[116]

Trps1$^{\Delta int/\Delta int}$ mice show delayed SOC formation.[110] SOC appeared after the formation of the primary ossification center and separated the articular cartilage and growth plate cartilage (Figure 4B). Recent evidence suggests that SOC reduces mechanical stress on the epiphyseal growth plate and protects chondrocytes from apoptosis.[117] As the elongation of long bones relies on normal growth plate functions, the growth failure observed in *Trps1*$^{\Delta int/\Delta int}$ mice may have been caused by excessive mechanical stress on the epiphysis because of delayed SOC formation.

4 | ANIMAL MODELS SHOWING CHROMOSOMAL INVERSION NEAR TRPS1 LOCUS

In this section, we describe animal models that exhibit *Trps1* reduction but display different phenotypes from *Trps1* mutant strains.

4.1 | Koala mice (Koa) and hairy-eared mice (Eh)

Koa and Eh mouse strains were independently developed using irradiation-mediated mutagenesis study at the Misr Radiology Center and Oak Ridge National Laboratory, respectively. Linkage analysis of the Koa mouse mutation mapped the candidate gene locus to the distal half of mouse chromosome 15.[118,119] More recently, specific inversion breakpoints spanning approximately 32 Mb on chromosome 15 have been identified (Figure 7).[120] Chromosomal inversion often results in developmental defects,[121,122] usually caused by the disruption or altered expression of genes located in the vicinity of inversion breakpoints.[123,124] Indeed, Koa inversion has been shown to result in a positional effect (alteration in gene expression caused by changes in the position of a gene relative to its native chromosomal region), which significantly reduces *Trps1* expression levels in the whole body at the embryonic stage and in hair follicles at postnatal stages.[53,125,126]

Similar to the mutations in Koa mice, Eh mutations are associated with a paracentric inversion of the distal half of chromosome 15.[127–129] The specific Eh inversion locus (Figure 7) largely overlaps with the Koa inversion locus, although the expression of *Trps1* in Eh mice has not been examined in detail.[125,128] The mouse gene loci where Koa and Eh inversions on distal chromosome 15 have been mapped are in a region syntenic to human chromosome 8q.[120] Interestingly, Ambras syndrome, which is a rare form of congenital hypertrichosis with excessive hair on the shoulders, face, and ears, is associated with chromosomal rearrangements of human chromosome 8q.[130] Indeed, 11.5 Mb candidate intervals for Ambras syndrome on chromosome 8q have been identified as cytogenic breakpoints in patients.[125] TRPS1 expression is either absent or has significantly decreased levels in all patient lymphoblast samples examined.[125]

4.1.1 | Hair follicle phenotypes

In Koa mice, the expression level of *Trps1* is significantly reduced in back skin samples containing hair follicles.[53,125,126] Adult Koa mice have long hair on both surfaces of the pinnae and around the muzzle.[125] In contrast, the vibrissa follicles (consisting of large follicles) are sparse and reduced in number compared to that in control mice.[125] Thus, while loss of TRPS1 function due to intragenic mutations leads to sparse, fine hair in more than 90% of human cases, reduced expression levels of *Trps1* due to positional effects can result in excessive and ectopic hair growth. The mechanisms underlying hypertrichosis in Koa mice, despite the reduced *Trps1* levels, require further investigation. As described above, the expression levels of *Trps1* in various tissues of Eh mice have not been examined in previous studies; however, ectopic *Hoxc5* expression has been reported.[128]

4.1.2 | Craniofacial and long bone phenotypes

Koa/Koa homozygous mice show mild spinal curvature,[125] deformed ribs, shortened skull length with abnormally thick zygomatic arches, and reduced long bone length.[126] Koa/Koa mice also display growth retardation that becomes prominent after birth.[126] Reduced *Trps1* expression levels have been observed in Koa/+ and Koa/Koa mice compared to control wild-type mice.[126]

Scoliosis (30%), a narrow palate (70%), micrognathia (25%), short metatarsals and metacarpals (60%), and brachydactyly (70%) are some of the commonly observed features in patients with TRPS.[5] The skeletal phenotypes of Koa/Koa mice somewhat resemble those observed in human patients with TRPS; however, in patients with Ambras syndrome, in which *TRPS1* is assumed to be significantly downregulated, the cardinal features of TRPS (sparse hair, cone-shaped epiphysis, and short stature) are not observed.[130] As humans with Ambras syndrome and Koa mice possess a relatively large genomic inversion, it is expected that other genes might be affected in addition to *TRPS1* (Figure 8).

5 | THE PHENOTYPES OF THE HUMAN DISORDERS WHOSE CAUSATIVE GENES ARE ALTERED IN *TRPS1* MUTANT STRAINS

In this section, we summarize human disorders of which the causative genes have been shown to be involved in pathologies observed in *Trps1* mutants. In the long bones, interactions between Trps1 and Gli3 have been intensively studied, while Wnt5a has been identified as one of the downstream targets of Trps1.

5.1 | Greig cephalopolysyndactyly syndrome (OMIM 175700) and Pallister-Hall syndrome (OMIM 146510)

The phenotypic spectrum of *GLI3* mutations in humans includes autosomal dominant Greig-cephalopolysyndactyly syndrome (GCPS) and Pallister-Hall syndrome (PHS).[131] Patients with GCPS typically display polysyndactyly of the hands and feet, together with several craniofacial features (macrocephaly, ocular hypertelorism, and a prominent forehead). PHS is described as a neonatally lethal condition associated with hypothalamic hamartoma, postaxial or central polydactyly, anal atresia, and bifid epiglottis.[132,133] A robust genotype–phenotype correlation of GLI3 mutations has been demonstrated.[134,135] Haploinsufficiency of GLI3 causes GCPS because of the loss of protein activity, whereas truncating mutations in the middle third of the gene generally cause PHS, resulting in a constitutive GLI3 repressor protein.[134,136,137]

5.2 | Robinow syndrome (OMIM268310) and brachydactyly type B1 (BDB1; OMIM113000)

Wnt5a has been identified as one of the downstream targets of Trps1 and Gli3 mediated transcription in the long bone growth plate.[64] However, mutations in WNT5A signaling molecules result in much more severe pathologies compared to TRPS1 or GLI3 mutations. Robinow syndrome and brachydactyly type B1 (BDB1) are skeletal disorders caused by mutations in WNT5A and ROR2, a co-receptor of WNT5A.[138–142] Patients with Robinow syndrome display mesomelic limb shortening and dwarfism but are also characterized by broad skeletal pathologies.[139,143] Robinow syndrome is caused by homozygous missense, nonsense, and frameshift mutations in either the extracellular or cytoplasmic region of ROR2, whereas BDB1 is caused by heterozygous mutations that truncate the cytoplasmic portion of ROR2.

6 | FUTURE PERSPECTIVES AND UNANSWERED QUESTIONS

A large number of studies have revealed pathologies of TRPS and etiologies of pathogenesis through analyses of mouse models for TRPS as well as examinations of human patients. However, there still remain critical issues, as shown below, which need to be addressed in future TRPS studies.

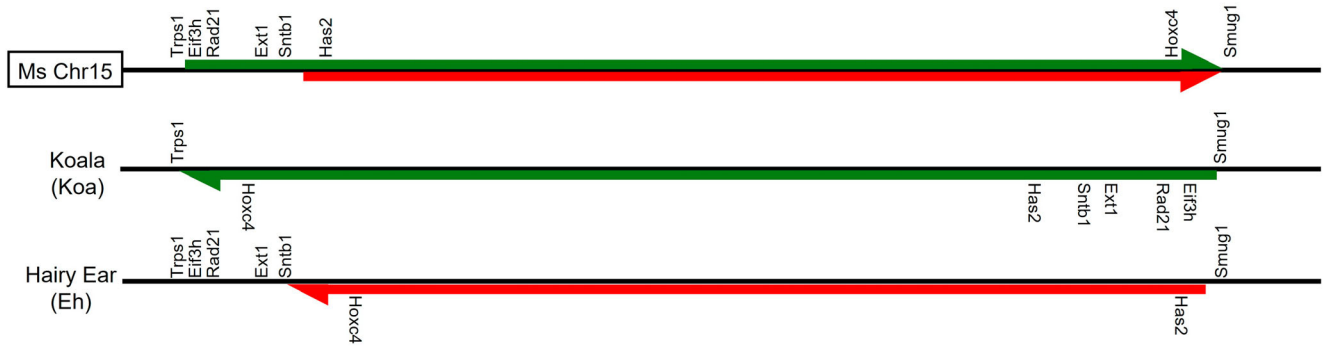


FIGURE 8 Genomic structures of Koa and Eh mice. The inversion breakpoints of Koa and Eh mouse strains are shown.

1. It is important to develop sophisticated methods for analyzing modest phenotypes for mouse studies. Subtle phenotypes might be present in heterozygous *Trps1*-mutant mice being overlooked. Also, it is necessary to develop animal models of TRPS II and TRPS III.
2. Animal models of TRPS1 are ready for preclinical studies on prenatal and postnatal pathologies. Especially, short stature observed in postnatal Trps1$^{\Delta int}$ mice can be used for investigating the effects of growth hormone therapy (which is still controversial for use in TRPS patients). Furthermore, the drugs such as meclizine and statins, which have been proved to be effective in the treatment of achondroplasia (dwarf) mouse models, could also be tested in TRPS disease models.
3. The discrepancies between human TRPS and mouse *Trps1* mutants require further investigation.

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DATA AVAILABILITY STATEMENT

Data sharing not applicable.

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REFERENCES

1. Giedion A. Tricho-rhino-phalangeal syndrome. *Helv Paediatr Acta*. 1966;21(5):475-485.
2. Langer LO. Thoracic-pelvic-phalangeal dystrophy—asphyxiating thoracic dystrophy of newborn infantile thoracic dystrophy. *Radiology*. 1968;91(3):447. doi:10.1148/91.3.447
3. Momeni P, Glockner G, Schmidt O, et al. Mutations in a new gene, encoding a zinc-finger protein, cause tricho-rhino--phalangeal syndrome type I. *Nat Genet*. 2000;24(1):71-74. doi:10.1038/71717
4. Ludecke HJ, Schaper J, Meinecke P, et al. Genotypic and phenotypic spectrum in tricho-rhino-phalangeal syndrome types I and III. *Am J Hum Genet*. 2001;68(1):81-91.
5. Maas SM, Shaw AC, Bikker H, et al. Phenotype and genotype in 103 patients with tricho-rhino-phalangeal syndrome. *Eur J Med Genet*. 2015;58(5):279-292. doi:10.1016/j.ejmg.2015.03.002
6. Langer LO, Krassikoff N, Laxova R, et al. The Tricho-rhino--phalangeal syndrome with exostoses (or Langer-Giedion syndrome)—4 additional patients without mental-retardation and review of the literature. *Am J Med Genet*. 1984;19(1):81-112. doi:10.1002/ajmg.1320190110
7. Hufeland M, Rahner N, Krauspe R. Trichorhinophalangeal syndrome type I: a novel mutation and Perthes-like changes of the hip in a family with 4 cases over 3 generations. *J Pediatr Orthop*. 2015;35(1):e1-5. doi:10.1097/BPO.0000000000000330
8. Itoh M, Kittaka Y, Niida Y, Saikawa Y. A novel frameshift mutation in the TRPS1 gene caused Tricho-rhino-phalangeal syndrome type I and III in a Japanese family. *Clin Pediatr Endocrinol*. 2016;25(3):115-118. doi:10.1297/cpe.25.115
9. Gilman JL, Newman HA, Freeman R, et al. Two cases of Legg-Perthes and intellectual disability in Tricho-rhino-phalangeal syndrome type 1 associated with novel TRPS1 mutations. *Am J Med Genet A*. 2017;173(6):1663-1667. doi:10.1002/ajmg.a.38204
10. Smaili W, Elalaoui SC, Meier S, Zerkaoui M, Sefiani A, Heinimann K. A novel TRPS1 mutation in a Moroccan family with Tricho-rhino-phalangeal syndrome type III: case report. *BMC Med Genet*. 2017;18(1):50. doi:10.1186/s12881-017-0413-8
11. Karaca A, Reyes M, Shumate LT, et al. Severe brachydactyly and short stature resulting from a novel pathogenic TRPS1 variant within the GATA DNA-binding domain. *Bone*. 2019;123:153-158. doi:10.1016/j.bone.2019.03.028
12. Levy-Shraga Y, Modan-Moses D, Wientroub S, Ovadia D, Zeitlin L. The effect of growth hormone treatment in a child with tricho-rhino-phalangeal syndrome: a case report and review of the literature. *Eur J Med Genet*. 2020;63(4):103830. doi:10.1016/j.ejmg.2019.103830
13. Wang C, Xu Y, Qing Y, et al. TRPS1 mutation detection in Chinese patients with Tricho-rhino-phalangeal syndrome and identification of four novel mutations. *Mol Genet Genom Med*. 2020;8(10):e1417. doi:10.1002/mgg3.1417
14. Ergoren MC, Akcan N, Manara E, et al. Characterization of a novel frameshift mutation within the TRPS1 gene causing Trichorhinophalangeal syndrome type 1 in a kindred Cypriot family. *Appl Immunohistochem Mol Morphol*. 2022;30(9):635-639. doi:10.1097/PAI.0000000000001056
15. Fang X, Yang Q. A missense mutation in TRPS1 in a family with Trichorhinophalangeal syndrome type III accompanied by ankylosing spondylitis. *Ann Dermatol*. 2022;34(2):139-143. doi:10.5021/ad.2022.34.2.139
16. Huang Q, Jiang C, Sun J, Xue J, Zhang VW. Case report: a novel mutation in TRPS1 identified in a Chinese family with tricho-rhino-phalangeal syndrome I: a therapeutic challenge. *Front Pediatr*. 2022;10:990230. doi:10.3389/fped.2022.990230
17. Ozturk N, Karamik G, Mutlu H, et al. Expanding the clinical and molecular features of trichorhino- phalangeal syndrome with a novel variant. *Turk J Pediatr*. 2023;65(1):81-95. doi:10.24953/turkjped.2022.793
18. Yagasaki H, Narusawa H, Watanabe D, et al. Novel TRPS1 frameshift variant in tricho-rhino-phalangeal syndrome type I accompanied by zinc deficiency. *Eur J Med Genet*. 2023;66(12):104870. doi:10.1016/j.ejmg.2023.104870
19. Herlin LK, Herlin MK, Blechingberg J, et al. Clinical presentation and genetics of tricho-rhino-phalangeal syndrome (TRPS) type 1: a single-center case series of 15 patients and seven novel TRPS1 variants. *Eur J Med Genet*. 2024;69:104937. doi:10.1016/j.ejmg.2024.104937

20. Bennassar A, Ferrando J, Grimalt R. Congenital atrichia and hypotrichosis. *World J Pediatr*. 2011;7(2):111-117. doi:10.1007/s12519-011-0262-z
21. Ito T, Shimomura Y, Farooq M, Suzuki N, Sakabe J, Tokura Y. Trichorhinophalangeal syndrome with low expression of TRPS1 on epidermal and hair follicle epithelial cells. *J Dermatol*. 2013;40(5):396-398. doi:10.1111/1346-8138.12111
22. Schacht V, Borelli D, Tsambaos D, Spycher MA, Trueb RM. Das Trichirhinophalangeal Syndrome Fall beispiel nit Untersuchung der biophy si kalischen Haarschaft parameter. *Hautarzt*. 2001;52:51-55.
23. Bennett CG, Hill CJ, Frias JL. Facial and oral findings in trichorhinophalangeal syndrome type 1 (characteristics of TRPS 1). *Pediatr Dent*. 1981;3(4):348-352.
24. King GJ, Frias JL. A cephalometric study of the craniofacial skeleton in trichorhinophalangeal syndrome. *Am J Orthod*. 1979;75(1):70-77. doi:10.1016/0002-9416(79)90140-4
25. Hallett SA, Zhou A, Herzog C, Arbiv A, Ono W, Ono N. Cranial base synchondrosis lacks PTHrP-expressing column-forming chondrocytes. *Int J Mol Sci*. 2022;23(14):7873. doi:10.3390/ijms23147873
26. Melsen B. Time and mode of closure of the spheno-occipital synchrondrosis determined on human autopsy material. *Acta Anat*. 1972;83(1):112-118. doi:10.1159/000143852
27. Unger S, Ferreira CR, Mortier GR, et al. Nosology of genetic skeletal disorders: 2023 revision. *Am J Med Genet A*. 2023;191(5):1164-1209. doi:10.1002/ajmg.a.63132
28. Beals RK. Tricho-rhino-phalangeal dysplasia. Report of a kindred. *J Bone Joint Surg Am*. 1973;55(4):821-826.
29. Cope R, Beals RK, Bennett RM. The trichorhinophalangeal dysplasia syndrome: report of eight kindreds, with emphasis on hip complications, late presentations, and premature osteoarthrosis. *J Pediatr Orthop*. 1986;6(2):133-138.
30. Ackert-Bicknell CL, Demissie S, Tsaih SW, et al. Genetic variation in TRPS1 may regulate hip geometry as well as bone mineral density. *Bone*. 2012;50(5):1188-1195. doi:10.1016/j.bone.2012.01.011
31. Dunbar JD, Sussman MD, Aiona MD. Hip pathology in the trichorhinophalangeal syndrome. *J Pediatr Orthop*. 1995;15(3):381-385. doi:10.1097/01241398-199505000-00023
32. Pavone V, Chisari E, Vescio A, Lizzio C, Sessa G, Testa G. Aetiology of Legg-calve-Perthes disease: a systematic review. *World J Orthop*. 2019;10(3):145-165. doi:10.5312/wjo.v10.i3.145
33. Caldaci A, Testa G, Dell'Agli E, et al. Mid-long-term outcomes of surgical treatment of Legg-calve-Perthes disease: a systematic review. *Children*. 2022;9(8):1121. doi:10.3390/children9081121
34. Lecuire F. The long-term outcome of primary osteochondritis of the hip (Legg-calve-Perthes' disease). *J Bone Joint Surg*. 2002;84(5):636-640. doi:10.1302/0301-620x.84b5.12124
35. Joseph B. Natural history of early onset and late-onset Legg-calve-Perthes disease. *J Pediatr Orthop*. 2011;31(2 Suppl):S152-S155. doi:10.1097/BPO.0b013e318223b423
36. Cook PC. Transient synovitis, septic hip, and Legg-calve-Perthes disease: an approach to the correct diagnosis. *Pediatr Clin North Am*. 2014;61(6):1109-1118. doi:10.1016/j.pcl.2014.08.002
37. Schlesinger AE, Poznanski AK, Pudlowski RM, Millar EA. Distal femoral epiphysis: normal standards for thickness and application to bone dysplasias. *Radiology*. 1986;159(2):515-519. doi:10.1148/radiology.159.2.3961186
38. Weaver DD, Cohen MM, Smith DW. The tricho-rhino-phalangeal syndrome. *J Med Genet*. 1974;11(3):312-314. doi:10.1136/jmg.11.3.312
39. Robert SC, Cooper JP. A patient with tricho-rhino-phalangeal syndrome and mitral valve disease. *Int J Cardiol*. 2007;114(3):e129-e130. doi:10.1016/j.ijcard.2006.08.011
40. Sen G, Barendt E, Sinha M. Cardiac arrest in a patient with trichorhinophalangeal syndrome and dilated cardiomyopathy. *BMJ Case Rep*. 2021;14(2):e237604. doi:10.1136/bcr-2020-237604
41. Tasic V, Gucev Z, Ristoska-Bojkovska N, Janchevska A, Ludecke HJ. Tricho-rhino-phalangeal syndrome in a 13-year-old girl with chronic renal failure and severe growth retardation. *Ren Fail*. 2014;36(4):619-622. doi:10.3109/0886022X.2014.882237
42. Malik TH, Shoichet SA, Latham P, Kroll TG, Peters LL, Shivdasani RA. Transcriptional repression and developmental functions of the atypical vertebrate GATA protein TRPS1. *EMBO J*. 2001;20(7):1715-1725. doi:10.1093/emboj/20.7.1715
43. Georgopoulos K, Moore DD, Derfler B. Ikaros, an early lymphoid-specific transcription factor and a putative mediator for T cell commitment. *Science*. 1992;258(5083):808-812. doi:10.1126/science.1439790
44. Lowry JA, Atchley WR. Molecular evolution of the GATA family of transcription factors: conservation within the DNA-binding domain. *J Mol Evol*. 2000;50(2):103-115. doi:10.1007/s002399910012
45. Chang GT, van den Bemd GJ, Jhamai M, Brinkmann AO. Structure and function of GC79/TRPS1, a novel androgen-repressible apoptosis gene. *Apoptosis*. 2002;7(1):13-21.
46. Perdomo J, Crossley M. The Ikaros family protein Eos associates with C-terminal-binding protein corepressors. *Eur J Biochem*. 2002;269(23):5885-5892. doi:10.1046/j.1432-1033.2002.03313.x
47. Kaiser FJ, Brega P, Raff ML, et al. Novel missense mutations in the TRPS1 transcription factor define the nuclear localization signal. *Eur J Hum Genet*. 2004;12(2):121-126. doi:10.1038/sj.ejhg.5201094
48. Lentjes MH, Niessen HE, Akiyama Y, de Bruine AP, Melotte V, van Engeland M. The emerging role of GATA transcription factors in development and disease. *Expert Rev Mol Med*. 2016;18:e3. doi:10.1017/erm.2016.2
49. 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(7):915-921.
50. Kim J, Sif S, Jones B, et al. Ikaros DNA-binding proteins direct formation of chromatin remodeling complexes in lymphocytes. *Immunity*. 1999;10(3):345-355. doi:10.1016/s1074-7613(00)80034-5
51. Dege C, Hagman J. Mi-2/NuRD chromatin remodeling complexes regulate B and T-lymphocyte development and function. *Immunol Rev*. 2014;261(1):126-140. doi:10.1111/imr.12209
52. Fantauzzo KA, Christiano AM. Trps1 activates a network of secreted Wnt inhibitors and transcription factors crucial to

vibrissa follicle morphogenesis. *Development*. 2012;139(1):203-214. doi:10.1242/dev.069971

53. Fantauzzo KA, Kurban M, Levy B, Christiano AM. Trps1 and its target gene Sox9 regulate epithelial proliferation in the developing hair follicle and are associated with hypertrichosis. *PLoS Genet*. 2012;8(11):e1003002. doi:10.1371/journal.pgen.1003002
54. Rhee H, Polak L, Fuchs E. Lhx2 maintains stem cell character in hair follicles. *Science*. 2006;312(5782):1946-1949. doi:10.1126/science.1128004
55. Pennisi D, Gardner J, Chambers D, et al. Mutations in Sox18 underlie cardiovascular and hair follicle defects in ragged mice. *Nat Genet*. 2000;24(4):434-437. doi:10.1038/74301
56. Kiso M, Tanaka S, Saba R, et al. The disruption of Sox21-mediated hair shaft cuticle differentiation causes cyclic alopecia in mice. *Proc Natl Acad Sci USA*. 2009;106(23):9292-9297. doi:10.1073/pnas.0808324106
57. Vidal VP, Chaboissier MC, Lutzkendorf S, et al. Sox9 is essential for outer root sheath differentiation and the formation of the hair stem cell compartment. *Curr Biol*. 2005;15(15):1340-1351. doi:10.1016/j.cub.2005.06.064
58. Nowak JA, Polak L, Pasolli HA, Fuchs E. Hair follicle stem cells are specified and function in early skin morphogenesis. *Cell Stem Cell*. 2008;3(1):33-43. doi:10.1016/j.stem.2008.05.009
59. Wuelling M, Kaiser FJ, Buelens LA, et al. Trps1, a regulator of chondrocyte proliferation and differentiation, interacts with the activator form of Gli3. *Dev Biol*. 2009;328(1):40-53. doi:10.1016/j.ydbio.2009.01.012
60. Buscher D, Ruther U. Expression profile of Gli family members and Shh in normal and mutant mouse limb development. *Dev Dyn*. 1998;211(1):88-96. doi:10.1002/(SICI)1097-0177(199801)211:13.0.CO;2-3
61. Maynard TM, Jain MD, Balmer CW, LaMantia AS. High-resolution mapping of the Gli3 mutation extra-toes reveals a 51.5-kb deletion. *Mamm Genome*. 2002;13(1):58-61. doi:10.1007/s00335-001-2115-x
62. Koziel L, Wuelling M, Schneider S, Vortkamp A. Gli3 acts as a repressor downstream of Ihh in regulating two distinct steps of chondrocyte differentiation. *Development*. 2005;132(23):5249-5260. doi:10.1242/dev.02097
63. Napierala D, Sam K, Morello R, et al. Uncoupling of chondrocyte differentiation and perichondrial mineralization underlies the skeletal dysplasia in tricho-rhino-phalangeal syndrome. *Hum Mol Genet*. 2008;17(14):2244-2254. doi:10.1093/hmg/ddn125
64. Wuelling M, Schneider S, Schrother VA, Waterkamp C, Hoffmann D, Vortkamp A. Wnt5a is a transcriptional target of Gli3 and Trps1 at the onset of chondrocyte hypertrophy. *Dev Biol*. 2020;457(1):104-118. doi:10.1016/j.ydbio.2019.09.012
65. Yang Y, Topol L, Lee H, Wu J. Wnt5a and Wnt5b exhibit distinct activities in coordinating chondrocyte proliferation and differentiation. *Development*. 2003;130(5):1003-1015. doi:10.1242/dev.00324
66. Wang Y, Nathans J. Tissue/planar cell polarity in vertebrates: new insights and new questions. *Development*. 2007;134(4):647-658. doi:10.1242/dev.02772
67. Gray RS, Roszko I, Solnica-Krezel L. Planar cell polarity: coordinating morphogenetic cell behaviors with embryonic polarity. *Dev Cell*. 2011;21(1):120-133. doi:10.1016/j.devcel.2011.06.011
68. Halford MM, Armes J, Buchert M, et al. Ryk-deficient mice exhibit craniofacial defects associated with perturbed Eph receptor crosstalk. *Nat Genet*. 2000;25(4):414-418. doi:10.1038/78099
69. Wu J, Mlodzik M. A quest for the mechanism regulating global planar cell polarity of tissues. *Trends Cell Biol*. 2009;19(7):295-305. doi:10.1016/j.tcb.2009.04.003
70. Gao B, Song H, Bishop K, et al. Wnt signaling gradients establish planar cell polarity by inducing Vangl2 phosphorylation through Ror2. *Dev Cell*. 2011;20(2):163-176. doi:10.1016/j.devcel.2011.01.001
71. Andre P, Wang Q, Wang N, et al. The Wnt coreceptor Ryk regulates Wnt/planar cell polarity by modulating the degradation of the core planar cell polarity component Vangl2. *J Biol Chem*. 2012;287(53):44518-44525. doi:10.1074/jbc.M112.414441
72. Yamaguchi TP, Bradley A, McMahon AP, Jones S. A Wnt5a pathway underlies outgrowth of multiple structures in the vertebrate embryo. *Development*. 1999;126(6):1211-1223. doi:10.1242/dev.126.6.1211
73. DeChiara TM, Kimble RB, Poueymirou WT, et al. Ror2, encoding a receptor-like tyrosine kinase, is required for cartilage and growth plate development. *Nat Genet*. 2000;24(3):271-274. doi:10.1038/73488
74. Takeuchi S, Takeda K, Oishi I, et al. Mouse Ror2 receptor tyrosine kinase is required for the heart development and limb formation. *Genes Cells*. 2000;5(1):71-78. doi:10.1046/j.1365-2443.2000.00300.x
75. Qian D, Jones C, Rzadzinska A, et al. Wnt5a functions in planar cell polarity regulation in mice. *Dev Biol*. 2007;306(1):121-133. doi:10.1016/j.ydbio.2007.03.011
76. van den Bemd GJ, Jhamai M, Brinkmann AO, Chang GT. The atypical GATA protein TRPS1 represses androgen-induced prostate-specific antigen expression in LNCaP prostate cancer cells. *Biochem Biophys Res Commun*. 2003;312(3):578-584. doi:10.1016/j.bbrc.2003.10.154
77. Asou N, Yanagida M, Huang L, et al. Concurrent transcriptional deregulation of AML1/RUNX1 and GATA factors by the AML1-TRPS1 chimeric gene in t(8;21)(q24;q22) acute myeloid leukemia. *Blood*. 2007;109(9):4023-4027. doi:10.1182/blood-2006-01-031781
78. Hong J, Sun J, Huang T. Increased expression of TRPS1 affects tumor progression and correlates with patients' prognosis of colon cancer. *Biomed Res Int*. 2013;2013:454085. doi:10.1155/2013/454085
79. Liang H, Cheung LW, Li J, et al. Whole-exome sequencing combined with functional genomics reveals novel candidate driver cancer genes in endometrial cancer. *Genome Res*. 2012;22(11):2120-2129. doi:10.1101/gr.137596.112
80. Radvanyi L, Singh-Sandhu D, Gallichan S, et al. The gene associated with trichorhinophalangeal syndrome in humans is overexpressed in breast cancer. *Proc Natl Acad Sci USA*. 2005;102(31):11005-11010. doi:10.1073/pnas.0500904102
81. Lennartz M, Lohr N, Hoflmayer D, et al. TRPS1 is a highly sensitive marker for breast cancer: a tissue microarray study evaluating more than 19,000 tumors from 152 different tumor entities. *Am J Surg Pathol*. 2024;48(6):637-651. doi:10.1097/PAS.0000000000002213

82. Ai D, Yao J, Yang F, et al. TRPS1: a highly sensitive and specific marker for breast carcinoma, especially for triple-negative breast cancer. *Mod Pathol*. 2021;34(4):710-719. doi:10.1038/s41379-020-00692-8
83. Lui JW, Tsang JY, Li J, et al. TRPS1 is a promising marker for all subtypes of breast cancer. *Histopathology*. 2024;84(5):822-836. doi:10.1111/his.15126
84. Chen JQ, Litton J, Xiao L, et al. Quantitative immunohistochemical analysis and prognostic significance of TRPS-1, a new GATA transcription factor family member, in breast cancer. *Horm Cancer*. 2010;1(1):21-33. doi:10.1007/s12672-010-0008-8
85. Serandour AA, Mohammed H, Miremadi A, Mulder KW, Carroll JS. TRPS1 regulates oestrogen receptor binding and histone acetylation at enhancers. *Oncogene*. 2018;37(39):5281-5291. doi:10.1038/s41388-018-0312-2
86. Wang Y, Lin X, Gong X, et al. Atypical GATA transcription factor TRPS1 represses gene expression by recruiting CHD4/NuRD(MTA2) and suppresses cell migration and invasion by repressing TP63 expression. *Oncogene*. 2018;7(12):96. doi:10.1038/s41389-018-0108-9
87. Liu-Chittenden Y, Huang B, Shim JS, et al. Genetic and pharmacological disruption of the TEAD-YAP complex suppresses the oncogenic activity of YAP. *Genes Dev*. 2012;26(12):1300-1305. doi:10.1101/gad.192856.112
88. Dong J, Feldmann G, Huang J, et al. Elucidation of a universal size-control mechanism in drosophila and mammals. *Cell*. 2007;130(6):1120-1133. doi:10.1016/j.cell.2007.07.019
89. Li Z, Hao Q, Luo J, et al. USP4 inhibits p53 and NF-kappaB through deubiquitinating and stabilizing HDAC2. *Oncogene*. 2016;35(22):2902-2912. doi:10.1038/onc.2015.349
90. Wang Y, Zhang J, Wu L, et al. Tricho-rhino-phalangeal syndrome 1 protein functions as a scaffold required for ubiquitin-specific protease 4-directed histone deacetylase 2 de-ubiquitination and tumor growth. *Breast Cancer Res*. 2018;20(1):83. doi:10.1186/s13058-018-1018-7
91. Malik TH, Von Stechow D, Bronson RT, Shivdasani RA. Deletion of the GATA domain of TRPS1 causes an absence of facial hair and provides new insights into the bone disorder in inherited tricho-rhino-phalangeal syndromes. *Mol Cell Biol*. 2002;22(24):8592-8600.
92. Ishimori N, Stylianou IM, Korstanje R, et al. Quantitative trait loci for BMD in an SM/J by NZB/BlNJ intercross population and identification of Trps1 as a probable candidate gene. *J Bone Miner Res*. 2008;23(9):1529-1537. doi:10.1359/jbmr.080414
93. Ackert-Bicknell CL, Karasik D, Li Q, et al. Mouse BMD quantitative trait loci show improved concordance with human genome-wide association loci when recalculated on a new, common mouse genetic map. *J Bone Miner Res*. 2010;25(8):1808-1820. doi:10.1002/jbmr.72
94. Richards JB, Rivadeneira F, Inouye M, et al. Bone mineral density, osteoporosis, and osteoporotic fractures: a genome-wide association study. *Lancet*. 2008;371(9623):1505-1512. doi:10.1016/S0140-6736(08)60599-1
95. 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(12):1598-1604. doi:10.1002/ajmg.a.32348
96. 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(6):591-593. doi:10.1111/j.1399-0004.2010.01434.x
97. Cho KY, Kelley BP, Monier D, Lee B, Szabo-Rogers H, Napierala D. Trps1 regulates development of craniofacial skeleton and is required for the initiation of palatal shelves fusion. *Front Physiol*. 2019;10:513. doi:10.3389/fphys.2019.00513
98. Morioka D, Suse T, Shimizu Y, Ohkubo F, Hosaka Y. Langer-Giedion syndrome associated with submucous cleft palate. *Plast Reconstr Surg*. 1999;103(5):1458-1463. doi:10.1097/00006534-199904050-00015
99. Kronenberg HM. Developmental regulation of the growth plate. *Nature*. 2003;423(6937):332-336. doi:10.1038/nature01657
100. Suemoto H, Muragaki Y, Nishioka K, et al. Trps1 regulates proliferation and apoptosis of chondrocytes through Stat3 signaling. *Dev Biol*. 2007;312(2):572-581. doi:10.1016/j.ydbio.2007.10.001
101. Sun Y, Nakanishi M, Sato F, Oikawa K, Muragaki Y, Zhou G. Trps1 deficiency inhibits the morphogenesis of secondary hair follicles via decreased noggin expression. *Biochem Biophys Res Commun*. 2015;456(3):721-726. doi:10.1016/j.bbrc.2014.12.039
102. Zhang Y, Nakamura T, Furukawa F, Muragaki Y. Trps1-deficient transplanted skin gave rise to a substantial amount of hair: Trps1 is unnecessary for hair development. *Dermatol Rep*. 2019;11(1):7853. doi:10.4081/dr.2019.7853
103. Michikami I, Fukushi T, Honma S, et al. Trps1 is necessary for normal temporomandibular joint development. *Cell Tissue Res*. 2012;348(1):131-140. doi:10.1007/s00441-012-1372-1
104. Hinton RJ. Genes that regulate morphogenesis and growth of the temporomandibular joint: a review. *Dev Dyn*. 2014;243(7):864-874. doi:10.1002/dvdy.24130
105. Kunath M, Ludecke HJ, Vortkamp A. Expression of Trps1 during mouse embryonic development. *Mech Dev*. 2002;119-(Suppl 1):S117-S120.
106. Nishioka K, Itoh S, Suemoto H, et al. Trps1 deficiency enlarges the proliferative zone of growth plate cartilage by upregulation of Pthrp. *Bone*. 2008;43(1):64-71. doi:10.1016/j.bone.2008.03.009
107. Socorro M, Hoskere P, Roberts C, et al. Deficiency of mineralization-regulating transcription factor Trps1 compromises quality of dental tissues and increases susceptibility to dental caries. *Front Dent Med*. 2022;3:3. doi:10.3389/fdmed.2022.875987
108. Kantaputra PN, Coury SA, Tan WH. Impaired dentin mineralization, supernumerary teeth, hypoplastic mandibular condyles with long condylar necks, and a TRPS1 mutation. *Arch Oral Biol*. 2020;116:104735. doi:10.1016/j.archoralbio.2020.104735
109. Fujikawa K, Socorro M, Lukashova L, et al. Deficiency of Trps1 in Cementoblasts impairs Cementogenesis and tooth root formation. *Calcif Tissue Int*. 2024;115(5):686-699. doi:10.1007/s00223-024-01277-2
110. Saeki N, Inui-Yamamoto C, Ikeda Y, et al. Deletion of Trps1 regulatory elements recapitulates postnatal hip joint abnormalities and growth retardation of Trichorhinophalangeal syndrome in mice. *Hum Mol Genet*. 2024;33(18):1618-1629. doi:10.1093/hmg/ddae102

111. Sugiura Y. Tricho-rhino-phalangeal syndrome associated with Perthes-disease-like bone change and spondylolisthesis. *Jinrui Idengaku Zasshi*. 1978;23(1):23-30. doi:10.1007/BF01871379
112. Morris L, Kozlowski K, McNaught P, Silink M. Tricho-rhino-phalangeal syndrome I (report of 8 cases). *Australas Radiol*. 1985;29(2):167-173. doi:10.1111/j.1440-1673.1985.tb01685.x
113. Puliyel JM, Puliyel MM, Varughese S. The trichorhinophalangeal syndrome with repeated dislocation of the patella. *Clin Genet*. 1992;41(3):139-142. doi:10.1111/j.1399-0004.1992.tb03650.x
114. Bhashyam AR, Weaver MJ. Knee pain after a fall. *BMJ*. 2018;360:k775. doi:10.1136/bmj.k775
115. Grant JA. Editorial commentary: stabilize the patella to achieve functional gain but Don't neglect the cartilage that may cause long-term pain! Trochlear dysplasia plays a role in both. *Arthroscopy*. 2021;37(12):3477-3478. doi:10.1016/j.arthro.2021.06.015
116. Whittaker JL, Losciale JM, Juhl CB, et al. Risk factors for knee osteoarthritis after traumatic knee injury: a systematic review and meta-analysis of randomised controlled trials and cohort studies for the OPTIKNEE consensus. *Br J Sports Med*. 2022;56(24):1406-1421. doi:10.1136/bjsports-2022-105496
117. Xie M, Gol'din P, Herdina AN, et al. Secondary ossification center induces and protects growth plate structure. *eLife*. 2020;9:e55212. doi:10.7554/eLife.55212
118. Ball ST, Peters J. Koala, a dominant mutation. *Mouse News Lett*. 1989;83:163-164.
119. Peters J, Tease C, Ball ST. Koala, Koa, is associated with an inversion on mouse chromosome 15. *Genet Res*. 1992;59:237-238.
120. Katayama K, Furuno A, Miyamoto S, et al. Suppressed recombination on mouse chromosome 15 defined regions of chromosomal inversions associated with koala (koa) and hairy ears (eh) mutations. *Exp Anim*. 2008;57(1):73-77. doi:10.1538/expanim.57.73
121. Wise TL, Pravtcheva DD. Oligosyndactylism mice have an inversion of chromosome 8. *Genetics*. 2004;168(4):2099-2112. doi:10.1534/genetics.104.031914
122. Niedermaier M, Schwabe GC, Fees S, et al. An inversion involving the mouse Shh locus results in brachydactyly through dysregulation of Shh expression. *J Clin Invest*. 2005;115(4):900-909. doi:10.1172/JCI23675
123. Perry WL, Hustad CM, Swing DA, O'Sullivan TN, Jenkins NA, Copeland NG. The itchy locus encodes a novel ubiquitin protein ligase that is disrupted in a18H mice. *Nat Genet*. 1998;18(2):143-146. doi:10.1038/ng0298-143
124. Hagiwara N, Klewer SE, Samson RA, Erickson DT, Lyon MF, Brilliant MH. Sox6 is a candidate gene for p100H myopathy, heart block, and sudden neonatal death. *Proc Natl Acad Sci USA*. 2000;97(8):4180-4185. doi:10.1073/pnas.97.8.4180
125. Fantauzzo KA, Tadin-Strapps M, You Y, et al. A position effect on TRPS1 is associated with Ambras syndrome in humans and the koala phenotype in mice. *Hum Mol Genet*. 2008;17(22):3539-3551. doi:10.1093/hmg/ddn247
126. Katayama K, Miyamoto S, Furuno A, et al. Characterization of the chromosomal inversion associated with the Koa mutation in the mouse revealed the cause of skeletal abnormalities. *BMC Genet*. 2009;10:60. doi:10.1186/1471-2156-10-60
127. Davisson MT, Roderick TH, Akeson EC, Hawes NL, Sweet HO. The hairy ears (eh) mutation is closely associated with a chromosomal rearrangement in mouse chromosome 15. *Genet Res*. 1990;56(2–3):167-178. doi:10.1017/s0016672300035266
128. Katayama K, Furuno A, Akiyama K, Tsuji T, Kunieda T. Characterization of chromosomal inversion of the mouse hairy ears (eh) mutation associated with cleft palate. *Mamm Genome*. 2007;18(4):246-254. doi:10.1007/s00335-007-9015-7
129. Mentzer SE, Sundberg JP, Awgulewitsch A, et al. The mouse hairy ears mutation exhibits an extended growth (anagen) phase in hair follicles and altered Hoxc gene expression in the ears. *Vet Dermatol*. 2008;19(6):358-367. doi:10.1111/j.1365-3164.2008.00709.x
130. Baumeister FA, Egger J, Schildhauer MT, Stengel-Rutkowski S. Ambras syndrome: delineation of a unique hypertrichosis universalis congenita and association with a balanced pericentric inversion (8) (p11.2; q22). *Clin Genet*. 1993;44(3):121-128. doi:10.1111/j.1399-0004.1993.tb03862.x
131. Demurger F, Ichkou A, Mougou-Zerelli S, et al. New insights into genotype-phenotype correlation for GLI3 mutations. *Eur J Hum Genet*. 2015;23(1):92-102. doi:10.1038/ejhg.2014.62
132. Clarren SK, Alvord EC Jr, Hall JG. Congenital hypothalamic hamartoblastoma, hypopituitarism, imperforate anus, and postaxial polydactyly—a new syndrome? Part II: neuropathological considerations. *Am J Med Genet*. 1980;7(1):75-83. doi:10.1002/ajmg.1320070111
133. Hall JG, Pallister PD, Clarren SK, et al. Congenital hypothalamic hamartoblastoma, hypopituitarism, imperforate anus and postaxial polydactyly—a new syndrome? Part I: clinical, causal, and pathogenetic considerations. *Am J Med Genet*. 1980;7(1):47-74. doi:10.1002/ajmg.1320070110
134. Johnston JJ, Olivos-Glander I, Killoran C, et al. Molecular and clinical analyses of Greig cephalopolysyndactyly and Pallister-Hall syndromes: robust phenotype prediction from the type and position of GLI3 mutations. *Am J Hum Genet*. 2005;76(4):609-622. doi:10.1086/429346
135. Johnston JJ, Sapp JC, Turner JT, et al. Molecular analysis expands the spectrum of phenotypes associated with GLI3 mutations. *Hum Mutat*. 2010;31(10):1142-1154. doi:10.1002/humu.21328
136. Kang S, Graham JM Jr, Olney AH, Biesecker LG. GLI3 frameshift mutations cause autosomal dominant Pallister-Hall syndrome. *Nat Genet*. 1997;15(3):266-268. doi:10.1038/ng0397-266
137. Kalff-Suske M, Wild A, Topp J, et al. Point mutations throughout the GLI3 gene cause Greig cephalopolysyndactyly syndrome. *Hum Mol Genet*. 1999;8(9):1769-1777. doi:10.1093/hmg/8.9.1769
138. Afzal AR, Rajab A, Fenske CD, et al. Recessive Robinow syndrome, allelic to dominant brachydactyly type B, is caused by mutation of ROR2. *Nat Genet*. 2000;25(4):419-422. doi:10.1038/78107
139. Schwabe GC, Tinschert S, Buschow C, et al. Distinct mutations in the receptor tyrosine kinase gene ROR2 cause brachydactyly type B. *Am J Hum Genet*. 2000;67(4):822-831. doi:10.1086/303084
140. van Bokhoven H, Celli J, Kayserili H, et al. Mutation of the gene encoding the ROR2 tyrosine kinase causes autosomal recessive Robinow syndrome. *Nat Genet*. 2000;25(4):423-426. doi:10.1038/78113
141. Person AD, Beiraghi S, Sieben CM, et al. WNT5A mutations in patients with autosomal dominant Robinow syndrome. *Dev Dyn*. 2010;239(1):327-337. doi:10.1002/dvdy.22156

142. Wang B, Sinha T, Jiao K, Serra R, Wang J. Disruption of PCP signaling causes limb morphogenesis and skeletal defects and may underlie Robinow syndrome and brachydactyly type B. *Hum Mol Genet*. 2011;20(2):271-285. doi:10.1093/hmg/ddq462

143. Oldridge M, Fortuna AM, Maringa M, et al. Dominant mutations in ROR2, encoding an orphan receptor tyrosine kinase, cause brachydactyly type B. *Nat Genet*. 2000;24(3):275-278. doi:10.1038/73495

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