中山大學 中山眼科中心 ZHONGSHAN OPHTHALMIC CENTER, SUN YAT-SEN UNIVERSITY

Contents lists available at Lighthouse Scholar

EYE SCIENCE

journal homepage: journal.gzzoc.org.cn

doi: 10.12419/es24112602
View this article at: https://doi.org/10.12419/es24112602

• Review Article •

Research advancements in the clinical characteristics and pathogenic genes of LADD syndrome

Fei Wang (王菲)[1], Minghai Chen (陈铭海)[1, 2], Bingran Dong (董冰然)[1], Hai Tao (陶海)[1]

1. Senior Department of Ophthalmology, Chinese PLA General Hospital, Beijing 100039, China.
2. Criminal Investigation Detachment, Chaoyang District Branch of Beijing Public Security Bureau, Beijing 100025, China.

HIGHLIGHTS

1. Critical Discoveries and Outcomes

• In terms of the etiological mechanism, it identifies FGFR2, FGFR3, and FGF10 as the core pathogenic genes and clarifies the potential pathogenic mechanisms. Regarding clinical phenotypes, it systematically summarizes the diverse manifestations of the disease. Additionally, by comparing genetic characteristics with clinical symptoms, it points out the key differential features between lacrimo-auriculo-dento-digital (LADD) syndrome and similar diseases such as aplasia of the lacrimal and the major salivary glands (ALSG) and lethal lung developmental disorders (LLDD).

2. Methodological Innovations

• The combination of multi-dimensional phenotypic analysis and genetic testing enables a systematic review of multi-system symptoms, explores the associations between gene mutation sites and phenotypes, and facilitates improved diagnostic accuracy through disease differentiation.

3. Prospective Applications and Future Directions

• As a rare genetic disorder, LADD syndrome calls for in-depth exploration of the specific pathogenic pathways of gene mutations. Animal models can be used to verify the regulatory mechanisms of key signaling pathways, thereby providing a basis for the research and development of targeted therapies.

Abstract: LADD syndrome (lacrimo-auriculo-dento-digital syndrome, OMIM 149 730) is a rare autosomal dominant genetic disorder, also known as Levy-Hollister syndrome. It is characterized by multi-organ

Received date: 2024-11-26; **Revised date:** 2025-01-20; **Accepted date:** 2025-04-14; **Published online:** 2026-01-14

Corresponding author: Hai Tao, E-mail: taohaiwj@sina.com.

Full Text

abnormalities with interindividual variability. The core phenotypes involve multiple systems. In terms of ocular manifestations, 71% of patients present with lacrimal gland hypoplasia/agenesis, 50% with lacrimal punctum anomalies, and 71.4% with nasolacrimal duct obstruction; additional conditions such as corneal disorders and glaucoma may also occur. Ear anomalies include "cup ear" deformity, low-set ears, and hearing loss (affecting 59.1% of patients, mostly mild to moderate). Oral manifestations encompass enamel hypoplasia, microdontia, and salivary gland hypoplasia—with 65.7% of patients experiencing xerostomia during childhood. Rarely, urogenital, neurological, or pulmonary anomalies may develop. Pathogenically, the disease is caused by heterozygous mutations in fibroblast growth factor receptor 2 (FGFR2, the most common causative gene, particularly the IIIb subtype), FGFR3, or FGF10, which disrupts the FGF signaling pathway. Differential diagnosis can be performed based on phenotypic features and genetic testing. This study retrospectively analyzed clinical cases to systemize the phenotypes and pathogenic mechanisms of LADD syndrome, thereby deepening the understanding of its early diagnosis and future treatment strategies.

Keywords: LADD syndrome; genetic disease; pathogenic genes; gene therapy

Cite this article as: Wang F, Chen MH, Dong BR, Tao H. Research advancements in the clinical characteristics and pathogenic genes of LADD syndrome. Eye Science. 2026, 3(1): 37-53. doi: 10.12419/es24112602.

Introduction

LADD (lacrimo-auriculo-dento-digital) syndrome (OMIM, 149 730) is a rare genetic disorder, characterized by the abnormal development of multiple organs and systems.[1] Its distinctive features encompass lacrimal duct/gland hypoplasia or absence, dysplasia of the lacrimal duct, salivary gland hypoplasia, dental anomalies such as enamel hypoplasia, congenital tooth loss, microscopic teeth, and so on. It also abnormal ear morphology, hearing loss, and skeletal dysplasia. A growing body of literature suggests that certain patient populations may simultaneously exhibit facial dysmorphologies, neurological impairments, and renal developmental anomalies. The clinical phenotype of LADD syndrome shows significant variability among individuals, as well as notable racial and regional disparities.[2-4] Since Levy and Hollister first described this syndrome, it has also been known as Levy-Hollister syndrome (LHS).[5-7]

LADD syndrome is an autosomal dominant disorder, characterized by significant phenotypic variability. It is predominantly caused by heterozygous mutations in the fibroblast growth factor receptor 2 (FGFR2), FGFR3, or FGF10 genes. This condition is characterized by abnormalities in the FGFR signaling pathway. Among these genes, FGFR2 is the most frequently implicated pathogenic gene, with mutations predominantly affecting subtype IIIb. Clinical reports indicate that FGFR3 mutations are often associated with mild skeletal phenotypes, such as brachydactyly. Given the rarity of this disease and the incomplete understanding of the genotype- phenotype correlation in LADD syndrome, patients often encounter significant challenges in obtaining an accurate diagnosis and effective treatment during the early stages of the disease. However, with the progress of medical technology, particularly in genetic testing methods, our understanding of LADD syndrome continues to deepen, providing improved opportunities for diagnosis and treatment.

Clinical phenotype

Eyes

Hypoplasia of lacrimal gland

Based on existing literature, it has been reported that 71% of individuals diagnosed with LADD syndrome present developmental anomalies of the

lacrimal gland, making it one of the most common phenotypes. The use of magnetic resonance imaging (MRI) allows for effective visualization and assessment concerning abnormalities in size and morphology, including dysplasia or the complete absence of ducts or glandular tissues within this structure. Approximately 40% of these patients self-report subjective symptoms indicating reduced tear production. Furthermore, a subgroup of patients experiences a total lack of tear even during crying, which thus requires the prolonged use of artificial tears to relieve ocular discomfort. The insufficient production of tears also increases the susceptibility of certain patient populations to suffer from prolonged periods of chronic keratoconjunctivitis.[8-9]

Dysplasia of lacrimal duct

Congenital dysplasia of lacrimal duct has been documented in the early literature and is one of the most frequently reported ocular phenotypes.[5,10] Approximately 50% of patients with LADD syndrome may show an abnormal number or location of lacrimal punctum, with the absence of lacrimal punctum being a more prevalent phenotype. Additionally, about 71.4% of patients may present with nasolacrimal duct obstruction, which represents a more common phenotype of congenital lacrimal duct dysplasia.[3-4] In this study, it was found that 46.15% (6/13) of sporadic LADD syndrome patients reported in domestic and international literatures over the past two decades exhibited nasolacrimal duct obstruction. This condition was observed to have a higher prevalence compared to the absence of lacrimal punctum (3/13), as shown in Table 1. Patients with LADD syndrome and congenital lacrimal duct dysplasia typically present with childhood-onset epiphora symptoms. If accompanied by nasolacrimal duct obstruction or stenosis, the patient may exhibit manifestations of dacryocystitis, such as recurrent purulent discharge. Moreover, some patients may experience recurring conjunctivitis.[3,11-12] Santo RO et al.[11] reported a case of dacryocystocele in a 13-year-old female child, which was attributed to concurrent nasolacrimal duct obstruction and lacrimal punctum dysplasia. Furthermore, it has been observed that some patients may present with a lacrimal duct fistula, suggesting that it could also be considered one of the phenotypic manifestations associated with lacrimal duct dysplasia in LADD syndrome.[13-14] It is noteworthy that the presence of developmental defects in the lacrimal gland can lead to mild symptoms of epiphora, even in cases of lacrimal duct dysplasia. Therefore, relying solely on ocular symptoms may potentially result in misdiagnosis of congenital lacrimal duct dysplasia.

Others

The corneal abnormalities observed in patients with LADD syndrome include corneal epithelial erosion, neovascularization, and cornea thinning. The primary underlying pathological mechanism is the depletion of limbal stem cells, especially those expressing cytokeratin K3. Limbal stem cells serve as a source for the renewal and differentiation of corneal epithelial cells. Insufficient tear secretion due to lacrimal gland hypoplasia can exacerbate defects in the corneal epithelium, promote neovascularization, diminish sensation in affected individuals, and potentially lead to corneal ulcers that impair vision.[9,15-16]

The patient described by Tandon A et al.[17] in 2014 presented with LADD syndrome along with glaucoma, indicating that LADD syndrome may be a potential contributing factor to corneal thinning and the progression of glaucoma. This association could be attributed to gene mutations affecting the fibroblastic growth factor signaling pathway, which in turn may impact cellular proliferation and protein synthesis. Furthermore, other ocular developmental abnormalities documented in the literature include ptosis,[18-20] strabismus,[21-22] ocular hypertelorism,[2] entropion,[15,23] hypophasis, ophthalmoplegia,[15,24] microphthalmia, iris defects, etc. (Table 1-3). The aforementioned factors have a substantial impact on patients' visual acuity and daily functioning.

Ears

Ear morphological abnormalities, including microtia, a low-set ear position, and a small, round outer ear shape with a prominent upper edge, commonly referred as “cup ear”, are frequently documented phenotypic features in the literature on LADD syndrome. Studies have shown that

Table 1 Clinical manifestations of sporadic cases

Finding	Zhu H et al.[8]	Alhamadi R et al.[3]	Vicioni-Marques F et al.[2]	Pathivada L et al.[25]	Tandon A et al.[17]	Santo RO et al.[11]	Mathrawala NR et al.[21]	McKenna G et al.[18]	Caluff PR et al.[4]	Lehotay M et al.[26]	Haktanir B et al.[19]	Rohmann E et al.[27]	Moses JE et al.[12]
Gender	female	male	female	male	male	female	male	female	male	female	male	female	female
Age (Y)	4	18	13	7	30	13	7	12	13	23	14	?	1
Mutation	FGFR2 c.1874G>A											FGFR2 c.1882G > A	
Eyes													
aplasia of lacrimal glands	+	+		+		+	+		+			+	
stenosis/obstruction of the naso-lacrimal duct		+	+			+	+				+		+
dacryocystocele		+				+							
hypoplastic puncta		+										+	+
lacrimal duct fistula													
ptosis								+			+		
strabismus							+						
ocular hypertelorism			+										
keratopathy					+								
glaucoma					+								
Ears													
small or cup-shaped ear	+	+		+				+			+	+	+
low-set ear		+	+				+			+		+	+
hearing loss			+			+	+		+	+	+		+
Mouth													
microdontia					+			+			+	+	
enamel hypoplasia	+			+	+					+			
hypodontia	+		+					+				+	+
dental decay	+		+	+	+		+	+				+	
peg-shaped teeth		+			+							+	

Continued Table

Finding	Zhu H et al.[8]	Alhamadi R et al.[3]	Vicioni-Marques F et al.[2]	Pathivada L et al.[25]	Tandon A et al.[17]	Santo RO et al.[11]	Mathrawala NR et al. [21]	McKenna G et al. [18]	Caluff PR et al.[4]	Lehotay M et al. [26]	Haktanir B et al. [19]	Rohmann E et al.[27]	Moses JE et al. [12]
aplasia of the parotid glands	+	+		+			+		+	+	+		+
hypoplasia of the submandibular glands				+			+		+	+		+	
Skeleton													
polydactylism						+							+
syndactylia of fingers/toes		+								+			
short /Long phalanges		+									+		
clinodactyly	+		+				+	+					
absence of fingers/toes					+								
nail hypoplasia			+		+						+		
thumb hypoplasia			+		+							+	
galianconism			+										
cervical curvature abnormality													+
Others													
cardiac hypertrophy	+												
chronic malnutrition									+				
testicular edema							+						
agenesis of rib							+						
maxillofacial deformity										+			
hypocalcemia											+		
epilepsy											+		

"+"indicates that the patient presents with this particular clinical manifestation.

"?"denotes the absence of specific age information for this sporadic case in the original report.

Table 2 Clinical phenotypes observed in families with LADD syndrome

Finding	Hong-Yang Zhang et al.[14]	Wade EM et al.[28]	Ryu YH et al.[7]	Talebi F et al.[29]	Vila Perez D et al.[30]	Lim LT et al.[15]	Guven Y et al.[31]	Inan UU et al.[22]	Cortes M et al.[16]	Ramirez D et al.[32]
Mutation	FGF10 c.234dupC	FGF10 NC_000005.9: g.44300489_44312646del	FGFR2 c.1547C>T	FGFR3 c.1882G>A						
Eyes										
lacrimal duct fistula	2 (6)									
hypoplastic puncta	4 (6)	7 (8)		2 (2)			3 (3)			
obstruction of the nasolacrimal duct	1 (6)			2 (2)				2 (6)		1 (8)
aplasia of lacrimal glands			2(2)				3 (3)	1 (6)		
lacrimal duct obstruction					2 (6)					
entropion						1 (2)				
keratopathy						1 (2)			2 (2)	
hypophasis						1 (2)				
hyperopia						1 (2)				
diffuse ophthalmoplegia						2 (2)				
ptosis								1 (6)		
exotropia								1 (6)		
Ears										
low-set ear			1 (2)			1 (2)	2 (3)	1 (6)		
hearing loss			2 (2)	1 (2)			3 (3)	2 (6)		1 (8)
cup-shaped ear			1 (2)	1 (2)	1 (6)		1 (3)	1 (6)	1 (2)	6 (8)
Mouth										
dental decay		5 (8)	1 (2)		1 (6)			1 (6)	1 (2)	
hypoplasia of the submandibular/ parotid glands		2 (8)	2 (2)			1 (2)		3 (6)	1 (2)	1 (8)
enamel hypoplasia			1 (2)		5 (6)		1 (3)	2 (6)		3 (8)
hypodontia			1 (2)		1 (6)	1 (2)	2 (3)	4 (6)		
peg-shaped teeth					1 (6)		3 (3)			8 (8)
microdontia						1 (2)	1 (3)	1 (6)		

Continued Table

Finding	Hong-Yang Zhang et al.[14]	Wade EM et al.[28]	Ryu YH et al.[7]	Talebi F et al.[29]	Vila Perez D et al.[30]	Lim LT et al.[15]	Guven Y et al.[31]	Inan UU et al.[22]	Cortes M et al.[16]	Ramirez D et al.[32]
ankyloglossia							1 (3)			
Skeleton										
long phalanges	2 (6)									
polydactylism	1 (6)									
syndactylia of fingers/toes	3 (6)			2 (2)	1 (6)				2(2)	2 (8)
clinodactyly	1 (6)		1 (2)		5 (6)		2 (3)			1 (8)
hypoplastic thumb		3 (8)								
absence of toes/fingers					2 (6)				2 (2)	
toes curls					4 (6)					
nail dysplasia						1 (2)		2 (6)		
broad toes							3 (3)			1 (8)
short toes/fingers							1 (3)	3 (6)		2 (8)
duplicated thumb										6 (8)
decreased forearm pronation										3 (8)
symphalangism										4 (8)
radial aplasia										1 (8)
congenitally dislocated radial head										2 (8)
Others										
bifid uvula		1 (8)								
pulmonary acinar hypoplasia		1 (8)								
cryptorchidism			2 (2)							
cleft lip and palate					1 (6)					1 (8)
hypocalcemia								1 (6)		
epilepsy								2 (6)		
anosphrasia								1 (6)		
pyelonephritis										2 (8)
vesicoureteral refux										2 (8)
small scarred kidney										1 (8)
bicornuate uterus										1 (8)

The numbers in parentheses indicate the total patient count within each family

Table 3 Clinical phenotypes observed in families with LADD syndrome

Finding	Rohmann E et al.[27]					Milunsky JM et al.[33]		Hajianpour MJ et al.[34]	
	LADD-Ala	LADD-Ist	LADD-Le	LADD-Nij	LADD-Bo	Family 1	Family 2	Family 1	Family 2
mutation	FGFR3 c.1537G > A	FGFR2 c.1947-AGA-1949del	FGFR2 c.1882G > A	FGFR2 c.1882G > A	FGF10 c.317G > T	FGF10 c.467T > G	FGF10 c.409A > T	FGFR2 exon 15 and 16 deletion	c.401T>A
Eyes									
lacrimal duct fistula						+	+		
hypoplastic puncta	+	+	+		+	+	+		
aplasia of lacrimal glands	+	+	+		+				
lacrimal duct obstruction									+
strabismus						+		+	
epicanthus						+			
ocular Hypertelorism								+	
Ears									
low-set ear	+	+	+						
Hearing loss		+		+					
cup-shaped ear	+	+	+	+	+				
Mouth									
dental decay	+	+			+			+	+
hypoplasia of the submandibular/parotid glands			+						
enamel hypoplasia							+	+	
hypodontia	+		+					+	
peg-shaped teeth	+								
microdontia	+	+		+		+			
Skeleton									
syndactylia of fingers/toes			+					+	+
clinodactyly								+	+
hypoplastic thumb		+		+	+	+	+		
short toes/fingers								+	
Others									
craniofacial dysmorphic	+	+						+	+
nevus flammeus of the forehead								+	
joint hypermobility								+	
dry skin								+	
hypospadias								+	

"+" indicates that the patient presents with this particular clinical manifestation

approximately 70% of patients diagnosed with LADD syndrome display the characteristic "cup ear" feature.[3] In this study, we conducted a statistical analysis of 19 previously published family-based cases over the past two decades. The findings revealed that 12 of these cases presented with "cup ear", indicating a relatively high prevalence of this specific ear morphological abnormality among individuals diagnosed with LADD syndrome (see Table 2 and Table 3 for detailed information).

Furthermore, approximately 59.1% of patients diagnosed with LADD syndrome experience varying degrees of unilateral or bilateral hearing loss, including sensorineural deafness, conductive hearing loss, and mixed hearing loss.[3-4,22] The majority of patients have mild to moderate hearing impairment, while a minority suffer from severe hearing impairment.[18,35] Inner ear abnormalities are not a common cause of hearing loss in LADD syndrome.[36] Azar et al.[23] reported on patient with LADD syndrome who had inner ear malformations characterized by semicircular canal dysplasia. Meuschel-Wehner et al.[37] described a 13-year-old patient with LADD syndrome who exhibited bilateral dilation of the vestibular and semicircular canals, leading to hearing impairment. In 2013, Moses JE et al.[12] reported a case of bilateral cochlear dysplasia, in which the patient had a common cavity connecting the vestibular and external semicircular canals, along with the absence of an oval window. However, due to the patient's infancy, a detailed description of the hearing impairment was limited. Hearing loss, regardless of its underlying etiology, can directly contribute to developmental impairments in language and communication skills, as well as have significant negative impacts on social and mental health.

Mouth

The presence of LADD syndrome has a profound impact on the oral health of patients, as evidenced by the groundbreaking research conducted by Toumba et al.,[38] which provides a comprehensive characterization of the associated oral and dental anomalies. To date, the reported oral abnormalities encompass "nail teeth", dental deformities, microdontia, enamel hypoplasia, and tooth loss,[18,21,39] with enamel hypoplasia being the most prevalent condition.[35] Oral dysplasia not only affects the patient's appearance but also impairs chewing function and speech articulation. For instance, a study on oral health of patients with LADD syndrome revealed that poor enamel development reduces the teeth's resistance to acid erosion and wear, thereby increasing the challenges associated with tooth repair and treatment.[25] Moreover, inadequate dental cleaning which can be attributed to decreased salivation and abnormal enamel development, may contribute to persistent dental caries, as frequently mentioned in literature.[4,26]

Skeleton

Patients diagnosed with LADD syndrome present a variety of skeletal abnormalities that primarily affect the distal upper extremities, including polydactyly, syndactyly, ectrodactyly, elongated phalanges, and clinodactyly, which is characterized by lateral or medial curvature of the fingers.[35] The severity of these deformities varies, ranging from the common curvature of the fifth finger to the claw-like deformity that results from a combination of hypodactylia and clinodactyly. Short forearms, dysplasia of the wrist and elbow joints, as well as radioulnar fusion, may also be observed in these patients. Moreover, toe abnormalities are often manifested as shortened distal phalanges or syndactyly,[2-3,21,40] and some patients may exhibit cervical vertebrae fusion.[12]

The atypical facial development seen in patients with LADD syndrome is characterized by sunken facial contours and mandibular protrusion.[26] Carol Anne Murdoch-Kinch et al.[13] provided a comprehensive description of two cases of LADD syndrome, which included characteristic features such as cup-shaped ears and lacrimal duct fistula. Additionally, imaging examinations revealed temporomandibular joint dysplasia, a shortened mandibular ramus, protrusion of the hyoid bone, and an enlarged mandibular foramen. These findings significantly influenced the patients' facial morphology.

Salivary gland

Among the pathological features of LADD

syndrome, in addition to the abnormal development of the lacrimal gland, the syndrome is frequently accompanied by aberrant development of the parotid gland and submandibular gland. In clinical observations, unilateral or bilateral underdevelopment of the salivary glands is commonly seen, often leading to inadequate salivary secretion and dysphagia. According to research statistics, approximately 65.7% of patients with LADD syndrome have suffered from persistent xerostomia since childhood.[3] Due to a significant reduction in saliva production, the oral mucosa appears dry, and patients may exhibit the "mirror tongue" phenomenon.[8] The loss of saliva's cushioning effect, as well as its cleaning and antibacterial functions, further increases patients' susceptibility to severe periodontal disease and significantly elevates the risk of dental caries.[25,41] For these individuals, it is recommended to consider the lifelong use of saliva substitutes in conjunction with topical fluoride therapy, strict dietary control, and regular oral examinations as essential measures for preventing premature tooth loss.[21]

Additionally, it is important to note that in the majority of LADD syndrome cases, there is concurrent abnormal development of lacrimal and salivary glands, resulting in the manifestation of xerostomia and keratoconjunctivitis sicca from an early age. It is crucial to differentiate this condition from juvenile Sjogren's syndrome. Juvenile Sjogren's syndrome is an autoimmune disease that affects exocrine glands such as salivary and lacrimal glands. The initial symptom often presents as recurrent parotid gland swelling, which occurs more frequently than persistent xerostomia and keratoconjunctivitis sicca. Furthermore, a lip mucosal biopsy, along with the test for autoantibodies like antinuclear antibody (ANA), rheumatoid factor, or anti-SSA/SSB antibodies, holds significant diagnostic value.[20,42] Especially in young patients, precise identification of the aberrant manifestations of other organs and tissues associated with LADD syndrome, along with a comprehensive assessment of the functional status and morphological appearance of the affected exocrine glands, is imperative to avoid misdiagnosis.

Others

In addition to the aforementioned symptoms, LADD syndrome may also manifest with various other congenital abnormalities. According to literature reports, approximately 69.7% of individuals with LADD syndrome exhibit a range of urogenital anomalies, including renal dysplasia, renal arteriosclerosis, pyelectasis, and hydronephrosis.[3,43] Furthermore, a minority of patients may experience concurrent complications such as recurrent urinary tract infections, hypospadias, and vesicoureteral reflux.[35,44]

A small subset of patients may also present with congenital staphyloschisis, epiglottic dysplasia, hiatal hernia, and cleft lip and palate.[28-32] Additionally, individuals with LADD syndrome may develop neurosystemic disorders. In 2006, Inan UU et al.[22] reported a LADD family in which multiple patients were diagnosed with epilepsy (Table 2). In 2012, LT Lim et al.[15] described a 5-year-old child who exhibited ocular abnormalities including entropion, keratopathy, hypophasis, and diffuse ophthalmoplegia, alongside the typical symptoms of LADD syndrome, such as low-set ear, microdontia, salivary gland dysplasia, and short phalange. This provided new insights into the ocular manifestations of LADD syndrome. Additionally, patients with LADD syndrome may also have pulmonary acinar hypoplasia or bronchial abnormalities, which can be life-threatening in severe cases.[28]

Pathogenic genes and genetic information

Pathogenic genes

The pathogenic genes associated with LADD syndrome primarily include FGF10, FGFR2 and FGFR3. The fibroblast growth factors family encompasses a wide variety of proteins with diverse bioactivities. These proteins can promote fibroblast mitosis, mesodermal cell proliferation, and angiogenesis. FGF signaling is mediated by transmembrane tyrosine kinase receptors, which are encoded by four independent genes (FGFR1-4). These receptors are activated *via* heparan sulfate or Klotho-dependent pathways to carry out their biological

functions.[3,11,45]

Gene information

The FGF10 gene, also known as keratinocyte growth factor 2 (KGF2),[46] belongs to the FGF7 subfamily. It comprises a 627-base-pair full-length cDNA sequence that encodes a single-stranded polypeptide consisting of 208 amino acid residues. There is extensive documentation highlighting the crucial role of FGF10 in the morphogenesis of various organs, such as the limbs, the bronchopulmonary system, teeth, salivary glands, as well as in skin and adipose tissue development. As a paracrine factor, FGF10 effectively boosts FGFR2b signaling by activating the extracellular, transmembrane, and intracellular tyrosine kinase domains. The subsequent activation stimulates cell proliferation and matrix remodeling in glandular epithelial cell precursors. Additionally, it initiates the morphogenesis of multiple glands, including the lacrimal glands and salivary glands. The study by Rohmann E et al.[27]revealed a familial case of LADD syndrome associated with a mutation (c.317G > T) in the FGF10 gene. In this case, all patients exhibited abnormal lacrimal gland development. Milunsky JM et al.[33] reported a case involving a 3-year-old female patient who underwent genetic testing. The test confirmed the presence of a p.L156R missense mutation in the FGF10 gene. This mutation causes an alteration of a non-conserved amino acid, which may disrupt the binding between FGF10 and FGFR2b, thereby contributing to the development of the disease. In another family discussed in this article, the proband carried a nonsense mutation (FGF10: c.409A > T) located in exon 2. This mutation is predicted to lead to protein truncation by missing 73 amino acids. Consequently, it affects the interaction site between FGF10 and FGFR2b.

The FGFRs, which fall under the subclass of receptor tyrosine kinases (RTKs), constitute a family of proteins. Transcript alternative splicing of these proteins generates a wide variety of isoforms.These isoforms display specific binding affinities for distinct fibroblast growth factors (FGFs) and are expressed in diverse cellular environments. When FGFR bind to FGFs, it triggers receptor dimerization, which in turn initiates the phosphorylation of tyrosine kinase domains within the cell. This activation involves RAS, mitogen-activated protein kinases (MAPKs), extracellular signal-regulated kinases (ERKs), Src family kinases (SFKs), and subsequent phosphorylation events in the intracellular tyrosine kinase domains. Moreover, SFK, p38MAPKs, phospholipase Cγ (PLCγ), and other signaling pathways are also involved in these crucial signaling cascades that regulate cellular processes such as proliferation, differentiation, migration, and homeostasis maintenance.[12] All FGFR mutations identified so far in LADD syndrome are located within the tyrosine kinase domains of FGFR2 or FGFR3, specifically in loops that play a regulatory role in controlling tyrosine kinase activity.

The FGFR2 gene is composed of 24 exons, and the encoded FGFR2b protein gives rise to three receptor subtypes: FGFR2-IIIa, FGFR2-IIIb, and FGFR2-IIIc. Upon binding to their respective ligands, these isoforms form dimers and initiate downstream signaling pathways as mentioned previously.[47] LADD syndrome is associated with mutations in FGFR2-IIIb, a specific receptor for FGF10. These mutations lead to reduced tyrosine kinase activity, decreased substrate phosphorylation, and an impaired response in the MAPK signaling pathway. After conducting genetic testing on five families affected by LADD syndrome, Rohmann E et al.[27] discovered a heterozygous three-base deletion (D1947-AGA-1949) on exon 16 of the FGFR2 gene within the Turkish Ladd-IST family. This mutation results in an exchange between highly conserved arginine residues within the tyrosine kinase domain of FGFR2 and lysines. Additionally, they observed a heterozygous mutation (c.1882G > A) on exon 16 of the FGFR2 gene in both Dutch's LADD-Nij family and UK's LADD-Le family. This alteration is expected to substitute an extensively conserved alanine residue within the tyrosine kinase domain of FGFR2 with threonines. FGFR2 mutations are frequently implicated in Crouzon syndrome (OMIM:123 500) and Pfeiffer syndrome (OMIM:101 600). These syndromes are characterized by craniofacial abnormalities, with the

mutations predominantly occurring in the immunoglobulin-like domains IIIa and IIIc of the extracellular ligand-binding regions. It is crucial to distinguish these conditions from LADD syndrome.

The FGFR3 gene is situated on chromosome 4p16.3 and spans a genomic region of more than 16.5 kb, encompassing 19 exons. This gene encodes a highly conserved protein composed of 806 amino acids, which plays a pivotal role in fundamental cellular processes, including cell proliferation, wound healing, and angiogenesis. Similar to FGFR2, mutations in the FGFR3 gene are more frequently associated with skeletal growth disorders, such as thanatophoric dysplasia types I and II (OMIM 187 600) and achondroplasia (OMIM 100 800).[29] However, LADD syndrome caused by FGFR3 mutations is not linked to skeletal abnormalities. This difference may be due to the distinct activation profiles generated by different mutations. According to the existing literature, reports have indicated a difference in the pathogenesis of LADD syndrome between FGFR2 and FGFR3. Mutations within FGFR2 are mainly located in its activation loop, a region regulated by tyrosine kinase activity. In contrast, mutations within FGFR3 are primarily situated in the connecting loop of the tyrosine kinase domain.[33,48-49]

Differential diagnosis

Plasia of pacrimal and salivary glands syndrome, ALSG

ALSG represents a class of disorders primarily characterized by hypoplasia of the lacrimal and salivary glands. It has been suggested that LADD syndrome and ALSG are allelic disorders that stem from distinct types of FGF10 mutations, potentially representing different manifestations of an underlying common disorder.[33] Both LADD syndrome and ALSG can present with abnormal development of the lacrimal and salivary glands. Nevertheless, LADD syndrome demonstrates more complex clinical manifestations, which serves as a distinguishing factor between these two conditions (Table 4).

Table 4 Differential diagnosis essentials

Manifestations	Clinical Features	Pathogenic Genes	Identification Method
ALSG	hypoplasia of the lacrimal and salivary glands, abnormal development of lacrimal ducts	FGF10	seldom linked to bone abnormalities
LLDD	Insufficient respiratory function	FGF10, TBX4	without the typical manifestations of LADD, gene sequencing
BORS	hearing impairment, ear malformations, renal dysfunction	EYA1, SIX1	without the hypoplasia of the lacrimal and salivary glands, gene sequencing
ADULT	hypoplasia or aplasia of fingers and toes, multiple pigmented skin lesions, dental hypoplasia, abnormal development of lacrimal ducts, hypotrichosis, abnormalities in joint bones as well as fingernails and toenails	TP63	multiple pigmented skin lesions, hypotrichosis, gene sequencing

Lethal lung developmental disorders, LLDD

LLDD is a rare neonatal disorder distinguished by severe respiratory insufficiency, posing substantial challenges in clinical management. The established genetic causes include mutations in the FGF10 or TBX4 genes.[50] It is different from the pathogenesis

of LADD syndrome. The pathogenic mechanism by which FGF10 mutations lead to LLDD is attributed to haploinsufficiency. However, this process also requires additional genetic modifiers, such as non-coding variants within regulatory elements.[51] Secondly, dyspnea associated with LADD syndrome, resulting from alveolar dysplasia, has rarely been documented in the literature and is not considered a primary clinical manifestation. In summary, there are notable differences between the two conditions in terms of clinical presentations and pathogenic mechanisms.

Branchio-oto-renal syndrome, BORS

BORS syndrome is an autosomal dominant genetic disorder, characterized by hearing impairment, ear malformations, and renal dysfunction. The clinical manifestations of BORS syndrome, such as hearing loss, external ear deformities, and inner ear dysplasia, exhibit substantial similarities to those seen in LADD syndrome, which may potentially result in misdiagnosis. The main pathogenic genes associated with BORS syndrome include EYA1, SIX1, among others. Genetic testing of patients can aid in achieving an accurate diagnosis.[52-53]

Acro-dermato-ungual-lacrimal-tooth, ADULT

ADULT syndrome is a rare ectodermal dysplasia disorder that results from mutations in the TP63 gene.[54] Clinical features include hypoplasia or aplasia of fingers and toes, syndactyly of the toes, multiple pigmented skin lesions, dental hypoplasia, abnormal development of lacrimal ducts, hypotrichosis, as well as abnormalities in the joint bones, fingernails, and toenails.[55] Due to its phenotypic overlap with LADD syndrome, achieving an accurate diagnosis can be challenging. Nevertheless, genetic testing offers a reliable approach for differential diagnosis.

Summary

The clinical manifestations of LADD syndrome are diverse and multifaceted. As indicated by its nomenclature, the primary distinguishing features encompass lacrimal gland dysplasia or hypoplasia of the lacrimal duct system, auricular malformations, dental anomalies, and digital or pedal abnormalities. These characteristics constitute a critical diagnostic basis for identifying LADD syndrome. Additionally, LADD syndrome exhibits autosomal dominant inheritance, and genetic screening through gene sequencing serves as an indispensable diagnostic tool.

Due to the rarity of LADD syndrome, genetic testing is currently restricted to a relatively small cohort of patients, which impedes a comprehensive investigation into its pathogenic mechanisms. Given the complexity and significant variability in clinical manifestations, future research should focus on elucidating precise genotype-phenotype correlations. This will lay a solid foundation for identifying potential therapeutic targets by using animal models at a later stage. Simultaneously, a global case registry has been established to explore ethnic disparities and optimize clinical management strategies. This initiative is not only vital for the development of personalized treatment plans but also shows great promise for enhancing patients' quality of life.

Correction notice

None

Acknowledgements

None

Author contributions

(I) Conception and design: Hai Tao, Fei Wang
(II) Administrative support: Hai Tao
(III) Provision of study materials or patients: Fei Wang, Minghai Chen, Bingran Dong
(IV) Collection and assembly of data: Fei Wang, Minghai Chen, Bingran Dong
(V) Data analysis and interpretation: Fei Wang, Minghai Chen, Bingran Dong
(VI) Manuscript writing: All authors
(VII) Final approval of manuscript: All authors

Funding

This study was supported by the Youth Independent Innovation Scientific Research Fund Project of Chinese PLA General Hospital (22QNFC091).

Conflict of interests

None of the authors has any conflicts of interest to

disclose. All authors have declared in the completed the ICMJE uniform disclosure form.

Patient consent for publication

None

Ethical statement

None

Provenance and peer review

This article was s standard submission to our journal. The article has undergone peer review with our anonymous review system.

Data sharing statement

None

Open access statement

References

1. Ali MJ. Updates on congenital lacrimal drainage anomalies and their association with syndromes and systemic disorders: a major review. Ann Anat. 2021, 233: 151613. DOI: 10.1016/j.aanat.2020.151613.
2. Vicioni-Marques F, Meireles de Sousa SS, de Carvalho FK, et al. Orodental findings in patients with lacrimo-auriculo-dento-digital syndrome. J Dent Child (Chic). 2019, 86(1): 53-60.
3. Alhamadi R, Elkhamary SM, Maktabi A, et al. Lacrimo-auriculo-dento-digital syndrome: a case report and literature review. Saudi J Ophthalmol. 2022, 35(2): 152-158. DOI: 10.4103/1319-4534.337856.
4. Caluff PR, Silva AL, Mascaro VL, et al. The lacrimo-auriculo-dento-digital syndrome (LADD): case report and literature review. Arq Bras Oftalmol. 2009, 72(5): 715-718. DOI: 10.1590/s0004-27492009000500024.
5. Levy WJ. Mesoectodermal dysplasia. A new combination of anomalies. Am J Ophthalmol. 1967, 63(5): 978-982. DOI: 10.1016/0002-9394(67)90043-8.
6. Hollister DW, Klein SH, De Jager HJ, et al. The lacrimo-auriculo-dento-digital syndrome. J Pediatr. 1973, 83(3): 438-444. DOI: 10.1016/S0022-3476(73)80268-9.
7. Ryu YH, Kyun Chae J, Kim JW, et al. Lacrimo-auriculo-dento-digital syndrome: a novel mutation in a Korean family and review of literature. Mol Genet Genomic Med. 2020, 8(10): e1412. DOI: 10.1002/mgg3.1412.
8. Zhu H, Yu GY. Lacrimo-auriculo-dento-digital syndrome with AIRE mutation: a case report. J Stomatol Oral Maxillofac Surg. 2022, 123(6): e988-e990. DOI: 10.1016/j.jormas.2022.07.014.
9. Simpson A, Avdic A, Roos BR, et al. LADD syndrome with glaucoma is caused by a novel gene. Mol Vis. 2017, 23: 179-184.
10. Thompson E, Pembrey M, Graham JM. Phenotypic variation in LADD syndrome. J Med Genet. 1985, 22(5): 382-385. DOI: 10.1136/jmg.22.5.382.
11. Santo RO, Golbert MB, Akaishi PMS, et al. Giant dacryocystocele and congenital alacrimia in lacrimo-auriculo-dento-digital syndrome. Ophthalmic Plast Reconstr Surg. 2013, 29(3): e67-8. DOI: 10.1097/IOP.0b013e31826cb897.
12. Moses JE. Lacrimo-auriculo-dento-digital syndrome with unilateral inner ear dysplasia and craniocervical osseous abnormalities: case report and review of literature. Clin Neuroradiol. 2013, 23(3): 221-224. DOI: 10.1007/s00062-012-0170-1.
13. Murdoch-Kinch CA, Miles DA. Clinical and radiographic features of the lacrimo-auriculo-dento-digital syndrome. Oral Surg Oral Med Oral Pathol Oral Radiol Endodontology. 1996, 81(6): 727-735. DOI: 10.1016/S1079-2104(96)80080-1.
14. Zhang HY, Zhang CY, Wang F, et al. Identification of a novel mutation in the *FGF10* gene in a Chinese family with obvious congenital lacrimal duct dysplasia in lacrimo-auriculo-dento-digital syndrome. Int J Ophthalmol. 2023, 16(4): 499-504. DOI: 10.18240/ijo.2023.04.02.

15. Lim L T, Blum R, Chia S N, et al. Lacrimal-auricular-dental-digital (LADD) Syndrome with Diffuse Ophthalmoplegia-A New Finding. Semin Ophthalmol. 2012, 27(3-4): 59-60. DOI: 10.3109/08820538.2012.680639.
16. Cortes M, Lambiase A, Sacchetti M, et al. Limbal stem cell deficiency associated with LADD syndrome. Arch Ophthalmol. 2005, 123(5): 691-694. DOI: 10.1001/archopht.123.5.691.
17. Tandon A, Tehrani S, Greiner MA, et al. Thin central corneal thickness and early-onset glaucoma in lacrimo-auriculo-dento-digital syndrome. JAMA Ophthalmol. 2014, 132(6): 782-784. DOI: 10.1001/jamaophthalmol.2014.306.
18. McKenna GJ, Burke FM, Mellan K. Presentation of lacrimo-auriculo-dento-digital (LADD) syndrome in a young female patient. Eur Arch Paediatr Dent. 2009, 10(1): 35-39. DOI: 10.1007/BF03262698.
19. Haktanir A, Degirmenci B, Acar M, et al. CT findings of head and neck anomalies in lacrimo-auriculo-dento-digital (LADD) syndrome. Dentomaxillofac Radiol. 2005, 34(2): 102-105. DOI: 10.1259/dmfr/65931528.
20. Ostuni PA, Modolo M, Revelli P, et al. Lacrimo-auricolo-dento-digital syndrome mimicking primary juvenile Sjögren's syndrome. Scand J Rheumatol. 1995, 24(1): 55-57. DOI: 10.3109/03009749509095158.
21. Mathrawala NR, Hegde RJ. Lacrimo-auriculo-dento-digital syndrome. J Indian Soc Pedod Prev Dent. 2011, 29(2): 168-170. DOI: 10.4103/0970-4388.84693.
22. Inan UU, Yilmaz MD, Demir Y, et al. Characteristics of lacrimo-auriculo-dento-digital (LADD) syndrome: case report of a family and literature review. Int J Pediatr Otorhinolaryngol. 2006, 70(7): 1307-1314. DOI: 10.1016/j.ijporl.2005.12.015.
23. Azar T, Scott JA, Arnold JE, et al. Epiglottic hypoplasia associated with lacrimo-auriculo-dental-digital syndrome. Ann Otol Rhinol Laryngol. 2000, 109(8 Pt 1): 779-781. DOI: 10.1177/000348940010900814.
24. Wang F, Tao H, Han C. Research advances in pathogenic genes and clinical characteristics of congenital lacrimal passage dysplasia. Chinese Journal of Chinese Ophthalmology. 2016, 26(2): 131-136. DOI: 10.13444/j.cnki.zgzyykzz.2016.02.019.
25. Pathivada L, Krishna MK, Rallan M. A case of lacrimo-auriculo-dento-digital syndrome with multiple congenitally missing teeth. Case Rep Dent. 2016, 2016: 8563961. DOI: 10.1155/2016/8563961.
26. Lehotay M, Kunkel M, Wehrbein H. Lacrimo-auriculo-dento-digital syndrome. J Orofac Orthop / Fortschr Der Kieferorthopä die. 2004, 65(5): 425-432. DOI: 10.1007/s00056-004-0347-6.
27. Rohmann E, Brunner HG, Kayserili H, et al. Mutations in different components of FGF signaling in LADD syndrome. Nat Genet. 2006, 38(4): 414-417. DOI: 10.1038/ng1757.
28. Wade EM, Parthasarathy P, Mi J, et al. Deletion of the last two exons of FGF10 in a family with LADD syndrome and pulmonary acinar hypoplasia. Eur J Hum Genet. 2022, 30(4): 480-484. DOI: 10.1038/s41431-021-00902-0.
29. Talebi F, Ghanbari Mardasi F, Mohammadi Asl J, et al. Identification of a novel missence mutation in FGFR3 gene in an Iranian family with LADD syndrome by Next-Generation Sequencing. Int J Pediatr Otorhinolaryngol. 2017, 97: 192-196. DOI: 10.1016/j.ijporl.2017.04.016.
30. Vila Pérez D, Palanca Arias D, Gean Molins E, et al. Diagnóstico clínico de síndrome de levy-Hollister familiar. An De Pediatría. 2014, 80(2): 114-116. DOI: 10.1016/j.anpedi.2013.02.019.
31. Guven Y, Ozgur Rosti R, Bahar Tuna E, et al. Orodental findings of a family with lacrimo-auriculo-dento digital (LADD) syndrome. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2008, 106(6): e33-44. DOI: 10.1016/j.tripleo.2008.07.019.
32. Ramirez D, Lammer EJ. Lacrimoauriculodentodigital syndrome with cleft lip/palate and renal manifestations. Cleft Palate Craniofac J. 2004, 41(5): 501-506. DOI: 10.1597/03-080.1.

33. Milunsky JM, Zhao G, Maher TA, et al. LADD syndrome is caused by FGF10 mutations. Clin Genet. 2006, 69(4): 349-354. DOI: 10.1111/j.1399-0004.2006.00597.x.
34. Hajianpour MJ, Bombei H, Lieberman SM, et al. Dental issues in lacrimo-auriculo-dento-digital syndrome: an autosomal dominant condition with clinical and genetic variability. J Am Dent Assoc. 2017, 148(3): 157-163. DOI: 10.1016/j.adaj.2016.11.016.
35. Heinz GW, Bateman JB, Barrett DJ, et al. Ocular manifestations of the lacrimo-auriculo-dento-digital syndrome. Am J Ophthalmol. 1993, 115(2): 243-248. DOI: 10.1016/S0002-9394(14)73931-5.
36. Lemmerling MM, Vanzieleghem BD, Dhooge IJ, et al. The lacrimo-auriculo-dento-digital (LADD) syndrome: temporal bone CT findings. J Comput Assist Tomogr. 1999, 23(3): 362-364. DOI: 10.1097/00004728-199905000-00007.
37. Meuschel-Wehner S, Klingebiel R, Werbs M. Inner ear dysplasia in sporadic lacrimo-auriculo-dento-digital syndrome. A case report and review of the literature. ORL J Otorhinolaryngol Relat Spec. 2002, 64(5): 352-354. DOI: 10.1159/000066077.
38. Toumba KJ, Gutteridge DL. Lacrimo-auriculo-dento-digital syndrome: a literature review and case reports. Quintessence Int. 1995, 26(12): 829-839.
39. Tan J, Jones MLM, Teague WJ, et al. Craniofacial anomalies in a murine model of heterozygous fibroblast growth factor 10 gene mutation. Orthod Craniofac Res. 2024, 27(1): 84-94. DOI: 10.1111/ocr.12689.
40. Kreutz JM, Hoyme HE. Levy-Hollister syndrome. Pediatrics. 1988, 82(1): 96-99. DOI: 10.1007/978-1-4020-6754-9_9357.
41. Matsuda C, Matsui Y, Ohno K, et al. Salivary gland aplasia with cleft lip and palateA case report and review of the literature. Oral Surg Oral Med Oral Pathol Oral Radiol Endodontology. 1999, 87(5): 594-599. DOI: 10.1016/S1079-2104(99)70140-X.
42. Saad Magalhães C, de Souza Medeiros PB, Oliveira-Sato J, et al. Clinical presentation and salivary gland histopathology of paediatric primary Sjögren's syndrome. Clin Exp Rheumatol. 2011, 29(3): 589-593.
43. Roodhooft AM, Brussaard CC, Elst E, et al. Lacrimo-auriculo-dento-digital (LADD) syndrome with renal and foot anomalies. Clin Genet. 1990, 38(3): 228-232. DOI: 10.1111/j.1399-0004.1990.tb03574.x.
44. Shiang EL, Holmes LB. The lacrimo-auriculo-dento-digital syndrome. Pediatrics. 1977, 59(6): 927-930. DOI: 10.1007/978-3-540-95928-1_78.
45. Schütz K, Schmidt A, Schwerk N, et al. Variants in FGF10 cause early onset of severe childhood interstitial lung disease: a detailed description of four affected children. Pediatr Pulmonol. 2023, 58(11): 3095-3105. DOI: 10.1002/ppul.26627.
46. Emoto H, Tagashira S, Mattei MG, et al. Structure and expression of human fibroblast growth factor-10. J Biol Chem. 1997, 272(37): 23191-23194. DOI: 10.1074/jbc.272.37.23191.
47. Klint P, Claesson-Welsh L. Signal transduction by fibroblast growth factor receptors. Front Biosci. 1999, 4: D165-D177. DOI: 10.2741/klint.
48. Lew ED, Bae JH, Rohmann E, et al. Structural basis for reduced FGFR2 activity in LADD syndrome: Implications for FGFR autoinhibition and activation. Proc Natl Acad Sci USA. 2007, 104(50): 19802-19807. DOI: 10.1073/pnas.0709905104.
49. Shams I, Rohmann E, Eswarakumar VP, et al. Lacrimo-auriculo-dento-digital syndrome is caused by reduced activity of the fibroblast growth factor 10 (FGF10)-FGF receptor 2 signaling pathway. Mol Cell Biol. 2007, 27(19): 6903-6912. DOI: 10.1128/MCB.00544-07.
50. Vincent M, Karolak JA, Deutsch G, et al. Clinical, histopathological, and molecular diagnostics in lethal lung developmental disorders. Am J Respir Crit Care Med. 2019, 200(9): 1093-1101. DOI: 10.1164/rccm.201903-0495TR.
51. Karolak JA, Vincent M, Deutsch G, et al. Complex compound inheritance of lethal lung developmental disorders due to disruption of the TBX-FGF pathway. Am

J Hum Genet. 2019, 104(2): 213-228. DOI: 10.1016/j.ajhg.2018.12.010.

52. Ruf RG, Xu PX, Silvius D, et al. SIX1 mutations cause branchio-oto-renal syndrome by disruption of EYA1–SIX1–DNA complexes. Proc Natl Acad Sci U S A. 2004, 101(21): 8090-8095. DOI: 10.1073/pnas.0308475101.
53. Kochhar A, Fischer SM, Kimberling WJ, et al. Branchio-oto-renal syndrome. Am J Med Genet Part A. 2007, 143A(14): 1671-1678. DOI: 10.1002/ajmg.a.31561.
54. Berk DR, Armstrong NL, Shinawi M, et al. ADULT syndrome due to an R243W mutation in TP63. Int J Dermatol. 2012, 51(6): 693-696. DOI: 10.1111/j.1365-4632.2011.05375.x.
55. Prontera P, Garelli E, Isidori I, et al. Cleft palate and ADULT phenotype in a patient with a novel TP63 mutation suggests lumping of EEC/LM/ADULT syndromes into a unique entity: ELA syndrome. Am J Med Genet A. 2011, 155A(11): 2746-2749. DOI: 10.1002/ajmg.a.34270.