INTRODUCTION

Lacrimo-auriculo-dento-digital (LADD; OMIM#129730) syndrome is a rare autosomal dominantly inherited genetic disorder first described in 1973. (Hollister, Klein, De Jager, Lachman, & Rimoin, 1973, 1974; Levy, 1967). The term “LADD” was first introduced by Temtamy (1974). LADD syndrome is characterized by varying degrees of hypoplasia/aplasia of lacrimal ducts/glands, hypoplasia/aplasia of salivary glands, dental anomalies such as hypoplastic enamel, hypodontia, oligodontia, microdontia, inner and outer ear malformations, possible hearing loss, and digital anomalies.

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The current knowledge on LADD syndrome has been augmented by the identification of novel mutations in the associated genes, which has aided in the genetic diagnosis of affected individuals and families. The purpose of this report is to describe a novel mutation in a Korean family and to provide a review of existing literature on LADD syndrome.

Abstract

Background: Lacrimo-auriculo-dento-digital (LADD) syndrome is a rare autosomal dominant disorder caused by mutations in one of the three genes: fibroblast growth factor receptor 2 (FGFR2), FGFR3, or FGF10. Affected patients have hypoplasia/aplasia of lacrimal ducts/glands, hypoplasia/aplasia of salivary glands, dental anomalies, ear anomalies, hearing loss, and digital anomalies.

Case Presentation: Proband was an 11-year-old male with xerostomia, xerophthalmia, and a referring diagnosis of Sjogren syndrome. He presented with microdontia, hypodontia, low-set/cupped ear auricles, and hearing loss in the left ear.

Methods: Whole exome sequencing (WES) was performed on proband. Variations and segregation within the family were verified using Sanger sequencing.

Results: Molecular studies revealed a novel heterozygous missense mutation in exon 11 of FGFR2: c.1547C>T (p.Ala516Val), compatible with LADD syndrome.

Conclusion: To the best of our knowledge, this is the first report of a family with LADD syndrome in Korea. The combination of xerostomia and xerophthalmia, seen in patients with LADD syndrome, may be misdiagnosed as Sjogren syndrome. WES may be a useful clinical tool in ascertaining the affected gene in patients with suspected genetic disorders. Here, a literature review and summary of 23 case reports/series of LADD syndrome are presented, which may help to identify patients with this condition.

KEYWORDS
lacrimo-auriculo-dento-digital (LADD) syndrome, salivary gland agenesis, Sjogren syndrome, xerostomia
(Wiedemann & Drescher, 1986). Affected individuals complain of xerophthalmia with irritation or infection, xerostomia, dental caries, and dysphagia (Kreutz & Hoyme, 1988; Lacombe, Serville, Marchand, & Battin, 1993; Wiedemann & Drescher, 1986). Digital malformations include aplasia, hypoplasia, syndactyly, clinodactyly, or duplications (Hollister, Klein, De Jager, Lachman, & Rimoin, 1973; Levy, 1967).

This genetic disorder is caused by mutations in any of the three known genes, fibroblast growth factor receptor 2 (FGFR 2) (OMIM#134920), fibroblast growth factor receptor 3 (FGFR3) (OMIM#134934), and fibroblast growth factor 10 (FGF10) (OMIM#602115), which is the ligand of FGFR2 (Rohmann et al., 2006; Shams et al., 2007). Mutations in FGF10 also result in aplasia of the lacrimal and salivary glands (ALSG; OMIM#180920), an allelic disorder (Scheckenbach, Balz, Wagenmann, & Hoffmann, 2008). The diagnosis of LADD syndrome depends on clinical, radiologic, and genetic findings. The major features of LADD syndrome (xerostomia, xerophthalmia) may also be seen in Sjogren syndrome, which may lead to a misdiagnosis.

2 | CASE PRESENTATION

2.1 | Case description

Proband was an 11-year-old Korean male with a history of xerostomia. He initially visited a local dentist for dental caries, enamel hypoplasia, and hypodontia, and was referred to a pediatric rheumatologist under specific concerns for Sjogren syndrome. He had dry skin and xerophthalmia, allergic conjunctivitis, and barely shed tears. The patient had bilateral cryptotia and ear hypoplasia. He did not complain of any other neurologic, genitourinary, or gastrointestinal symptoms. His father was similarly affected but did not seek medical attention.

At the time of assessment, the patient weighed 33 kg (10 percentile) and was 141 cm tall (25 percentile). He had low-set, small, cup-shaped ears. An ophthalmic examination showed bilateral corneal punctate epithelial erosions, a bilateral tear break up time of 3 s, Schirmer test 3 and 4 mm for the right and left eye, respectively, and SICCA scores 4 and 5 for his right and left eye, respectively. There was no swelling of the parotid glands or submandibular glands. An intraoral examination showed a bald tongue and absence of the Stensen’s duct orifice in both buccal mucosae. A dental examination showed multiple caries, enamel hypoplasia, microdontia, and hypodontia (mandibular second premolars). Digital findings included clinodactyly of the second and third toes of both feet (Figure 1). There was no facial dysmorphism, nail dysplasia, or other malformations such as cleft lip or palate.

Laboratory routine investigations were all normal, including Anti-SSA/SSB antibodies. Ultrasonographic studies showed no identifiable submandibular or parotid gland structures, with small lymph nodes in its place. A contrast neck and orbit computed tomography scan showed no visible...
parotid glands, with small enhancing nodular lesions, possibly reactive lymph nodes, or hypoplastic submandibular glands (Figure 1-g). Audiometry revealed left sensorineural hearing loss.

2.2 | Ethical compliance

This study was independently reviewed and approved by the institutional review board of Seoul National University Dental Hospital and Seoul National University Hospital (H-1904-164-1031). Appropriate informed consent was obtained from all participating individuals and blood samples were collected according to the principles of the Declaration of Helsinki.

2.3 | Genetic analysis

Genomic DNA was isolated from peripheral blood samples of the proband and both of his parents. As a candidate gene approach, exons and intron-exon boundaries of FGFR10 were screened using Sanger sequencing, as previously described (Seymen et al., 2017). With no pathologic variant in FGFR10, WES was performed on the proband. Paired-end sequencing reads of 101 bp were obtained with the illumine HiSeq 2500 (Theragen Etex Bio Institute) after exome capturing with the Agilent SureSelect XT Human All Exon V5 Target Enrichment System. Sequencing reads were aligned to human reference genome hg19 and a series of bioinformatics analyses were performed as previously described (Koruyucu et al., 2018). Sanger sequencing was used to verify the genetic mutation in the proband and his father. In silico computational prediction analysis of variant was done to predict the pathogenic potential of the variant: Varsome (varsome.com) (Kopanos et al., 2019).

WES revealed a heterozygous novel missense mutation in exon 11 of FGFR2 (FGFR2: NM_022970.3): c.1547C>T (p.Ala516Val), compatible with the diagnosis of LADD syndrome. The novel variant and segregation within the family were verified using Sanger sequencing. His father had the same heterozygous missense mutation (Figure 2-b). The proband and his father were clinically and genetically diagnosed with LADD syndrome. This pathologic variant was submitted to the ClinVar database (submission ID: SUB6906532).

3 | DISCUSSION

To the best of our knowledge, this is the first report of a family with LADD syndrome in Korea. Both the patient and his father presented with xerostomia, cryptotia, and sensorineural hearing loss. Proband also had radiologically proven agenesis of parotid glands, no visible Stensen's duct orifices, dental malformations, xerophthalmia, and clinodactyly.

LADD syndrome, also known as Levy-Hollister syndrome, is a rare autosomal dominant genetic disorder, with varying degrees of anomaly penetration. Previously reported cases had indicated varied phenotypes, including facial dysmorphism, genitourinary and renal anomalies, gastrointestinal symptoms, skeletal involvement other than digital or limb involvement, and airway involvement. Twenty-three previous case reports and case series are summarized in Table 1 (Azar, Arnold, Scott, & Robin, 2000; Guven, Rosti, Tuna, Kayserili, & Aktoren, 2008; Hajianpour et al., 2017; Haktanir, Degirmenci, Acar, Albayrak, & Yucel, 2005; Hollister et al., 1973; Inan et al., 2006; Kreutz & Hoyme, 1988; Lacombe et al., 1993; Lehotay, Kunkel, & Wehrbein, 2004;
**TABLE 1** Review of literature on LADD syndrome

| Reference                        | F#(ind) | Age       | Family history | Involved organs | Involved organs | Gene                      | Pathologic variant                                |
|---------------------------------|---------|-----------|----------------|-----------------|-----------------|---------------------------|---------------------------------------------------|
| Levy (1967)                     | F1(1)   | 12 years  | −              | +               | +/−NR           | NR + + + +                | Congenital hip dislocation                         |
| Hollister et al. (1973)         | F1(6)   | 15 months | +              | +               | +/−NR           | NR + + + +                | Left renal agenesis                                |
|                                 |         | 4 years   | +              | +               | +/−NR           | NR + + + +                |                                                  |
|                                 |         | 6 years   | +              | +               | +/−NR           | NR + + + +                |                                                  |
|                                 |         | 11 years  | +              | −               | +/−NR           | NR + + + +                |                                                  |
|                                 |         | 17 years  | +              | +               | +/−NR           | NR + + + +                |                                                  |
|                                 |         | 43 years  | +              | +               | +/−NR           | NR + + + +                |                                                  |
| Shiang and Holmes (1977)        | F1(2)   | 21 y      | +              | +               | −/−             | + + + + +                 | Hypertension, nephrosclerosis                      |
|                                 |         | NR        | +              | +               | −/−             | − + + + +                 | Diabetes mellitus                                  |
| Thompson et al. (1985)          | F1(2)   | 6 years   | +              | +               | +/−NR           | + + + + +                 | Hiatus hernia, asthma                              |
|                                 |         | 32 years  | +              | +               | +/−NR           | + + + −                  | Stillbirth of second child                         |
| Kreutz and Hoyme (1988)         | F1(3)   | 9 years   | +              | +               | +/−NR           | NR + + + +                | Hyaline membranous disease, death                  |
|                                 |         | NR        | +              | −               | +/−NR           | NR + + + +                |                                                  |
|                                 |         | 18 hr     | +              | −               | +/−NR           | NR NR + +                |                                                  |
| Roodhooft et al. (1990)         |         | 11 years  | −              | +               | +/−NR           | − + + + +                | Caliectasis and lithiasis of kidneys, Henoch-Schonlein purpura with nephrotic syndrome |
| Lacombe et al. (1993)           | F1(2)   | 22 months | +              | +               | +/−NR           | NR + + + +                | Delayed psychomotor development, facial dysmorphism |
|                                 |         | 25 years  | +              | −               | −/−NR           | NR + + + +                | Split foot deformity, split hand deformity          |

(Continues)
| Reference                  | Age | Family history | Involved organs | Pathologic variant                                      |
|---------------------------|-----|----------------|-----------------|---------------------------------------------------------|
|                          |     |                | Lacrimal        | Auricular/Hearing | Salivary | Dental | Digital/Limb | Other | Gene | Pathologic variant |
| Ostuni et al. (1995)      |     |                | +              | +               | +/NR     | +      | +           | +     | Facial dysmorphism, ptosis, bifid uvula |
|                          | 24 years |                  |                |                |          |        |             |       |                  |
|                          | 4 years   |                  |                |                |          |        |             |       |                  |
| Azar et al. (2000)        | 5 years | −               | +              | +/+            | NR       | +      | +           | +     | Bilateral hydronephrosis, epiglottic hypoplasia, microglossia, undescended testicle, delayed psychomotor development |
| Meuschel-Wehner et al. (2002) | 13 years | −               | +              | −/+            | +        | +      | +           | +     | Scoliosis, inner ear dysplasia |
| Ramirez and Lammer (2004) |     |                |                |                |          |        |             |       |                  |
| F1(8)                     | 6 years | +              | −              | +/−            | +        | +      | +           | +     | Cleft lip and palate, Pneumothorax, pulmonary hypertension, PDA, bilateral hydronephrosis and vesicoureteral reflux |
|                          | 9 years | +              | −              | +/+            | NR       | +      | +           | +     | Vesicoureteral reflux, hydronephrosis, small scarred kidney, bicornuate uterus |
| NR                        |        |                | +              | +              | +/NR     | NR     | +           | +     |                  |
| NR                        |        |                | +              | −              | NR/NR    | NR     | +           | +     |                  |
| NR                        |        |                | +              | NR             | +/NR     | NR     | +           | +     |                  |
| NR                        |        |                | +              | −              | +/NR     | NR     | +           | +     | Arthritis (hands), Congenitally blind (unknown cause) |
| NR                        |        |                | +              | NR             | −/NR     | NR     | +           | +     |                  |
| Lehotay et al. (2004)     | 13 years | −      | NR             | +/+            | +        | +      | +           | +     | Midfacial hypoplasia, delayed speech development |

(Continues)
| Reference          | Age | Family history | Involved organs | Gene | Pathologic variant                          |
|-------------------|-----|----------------|-----------------|------|---------------------------------------------|
| Haktanir et al.   |     |                | Lacrimal        |      | Ptosis, nail dysplasia, epilepsy, hypocalcemia, basal ganglia calcification |
| (2005)            | 14 years | + |
|                   | NR | + |
|                   | NR | + |
|                   |     | NR |
|                   |     | NR |
|                   |     |   |
|                   |     |   |
| Rohmann et al.    |     |                | Auricular/     |      | Facial dysmorphism                          |
| (2006)            |     |                | Hearing        |      |                                             |
|                   | F1(7) | + |
|                   | F2(6) | + |
|                   | F3(6) | + |
|                   | F4(1) | + |
|                   | F5(4) | + |
|                   | F6(3) | + |
| Milunsky et al.   |     |                | Salivary       |      |                                             |
| (2006)            |     |                | Dental         |      |                                             |
|                   | F1(1) |     |
|                   | F2(2) | 19 years + |
|                   | F3(6) | + |
|                   | F4(1) | + |
|                   | F5(4) | + |
|                   | F6(3) | + |
|                   | F1(8) |     | Other          |      |                                             |
| Reference                  | Age       | Family history | Involved organs                     | Gene Pathologic variant                                                                 |
|----------------------------|-----------|----------------|-------------------------------------|----------------------------------------------------------------------------------------|
| Inan et al. (2006)         | 13 years  | +              | +/+/−                               | Facial dysmorphism, choanal atresia, ptosis, nail dysplasia, epilepsy, hypocalcemia      |
| NR                         | +         | −              | −/−                                 |                                                                                        |
| 19 years                   | +         | −              | −/+/−                               |                                                                                        |
| NR                         | +         | −              | +                                   |                                                                                        |
| 21 years                   | +         | +              | −/−                                 |                                                                                        |
| NR                         | +         | NR             | −/−                                 |                                                                                        |
| NR                         | +         | NR             | −/−                                 |                                                                                        |
| NR                         | +         | +              | +                                   |                                                                                        |
| Guven et al. (2008)        | 17 years  | +              | +/+/−                               |                                                                                        |
| 10 years                   | +         | +              | +/+/−                               |                                                                                        |
| 45 years                   | +         | +              | −/+/−                               |                                                                                        |
| McKenna et al. (2009)      | 12 years  | −              | −/−                                 |                                                                                        |
| Mathrawala and Hegde (2011)| 7 years   | −              | +/+/−                               |                                                                                        |
| Moses (2013)               | 1.4 years | −              | +/+/−                               |                                                                                        |
| Pathivada et al. (2016)    | 7 years   | NR             | +                                   |                                                                                        |
| Reference           | Age       | Family history | Involved organs | Digital/Limb | Other                          | Gene       | Pathologic variant |
|---------------------|-----------|----------------|-----------------|--------------|--------------------------------|------------|-------------------|
| Hajianpour et al.   | F1(3)     | 9 years        | + + −/− + + +   | Facial dysmorphism, FTT, joint hypermotility | FGFR2     | Exon 15 and 16 del |
|                     |           | 2 years        | + + −/− + − −   | Hypospadias, hypotonia, gross motor delay       | FGFR2     | Exon 15 and 16 del |
|                     | NR        | + + −/− + + +   | Strabismus, joint hypermobility                  | FGFR2     | Exon 15 and 16 del |
|                     | F2(3)     | 3 years        | + + +/− + + +   | Dolichocephaly, facial dysmorphism, micrognathia | FGF10     | c.401T>A (p.M134K) |
|                     | NR        | + + −/− + + +   | Eczematous dermatitis, toenail dysplasia          | FGF10     | c.401T>A (p.M134K) |
|                     | NR        | + + −/− + + +   | F1(2) 23 years  | + + +/− + + + | NR + + + NR Eczematous dermatitis, toenail dysplasia | FGFR3     | c.1882G>A (p.D628N) |
|                     |           | 10 years       | + + +/− + + +   | F2(3) 3 years | + + +/− + + + | FGFR2     | c.1547C>T (p.A516V) |
|                     | NR        | + NR NR NR + + + NR + + + NR | Present study (2020) | + + +/− + + + | | | |

Abbreviations: F#, family number; FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptors; ALSG, aplasia of the lacrimal and salivary glands; FTT, failure to thrive; ind, number of individuals; NR, not recorded; PDA, patent ductus arteriosus.
LADD syndrome may be genetically diagnosed, as it is known to be caused by mutations in *FGFR2*, *FGFR3*, and *FGF10* (Rohmann et al., 2006; Shams et al., 2007). In the current case, the proband and his father showed a pathologic mutation in *FGFR2*.

**FGFR2**
- **Gene**: *FGFR2*
- **Pathologic variant**: c.1947-AGA-1949 del (p.R649S_D650del)
- **Inheritance pattern**: AD
- **Phenotype**: Facial dysmorphism
- **Reference**: Rohmann et al. (2006)

**TABLE 2** Genotype phenotype correlation in LADD syndrome

| Gene   | Pathologic variant | Inheritance pattern | Phenotypea | Reference |
|--------|--------------------|----------------------|-------------|-----------|
| **FGFR2** | c.1947-AGA-1949 del (p.R649S_D650del) | AD | L(+) A/H(+/+) S(−)De(+), Di(+) | Facial dysmorphism, FTT, hypotonia, joint hypermotility, hypospadias, gross motor delay, strabismus | Rohmann et al. (2006) |
| | c.1942G>A (p.A648T) | AD | L(−) A/H(+/+) S(−)De(+), Di(+) | Facial dysmorphism | Rohmann et al. (2006) |
| | c.1942G>A (p.A648T) | AD | L(+) A/H(+/+) S(−)De(+), Di(+) | Facial dysmorphism | Rohmann et al. (2006) |
| | c.1882G>A (p.A628T) | De novo | L(+) A/H(+/+) S(−)De(+), Di(+) | Facial dysmorphism | Rohmann et al. (2006) |
| | Exon 15 and 16 del | AD | L(+) A/H(−/−) S(−)De(+) Di(+) | Facial dysmorphism, FTT, hypotonia, joint hypermotility, hypospadias, gross motor delay, strabismus | Hajianpour et al. (2017) |
| | c.1547C>T (p.A516V) | AD | L(+) A/H(+/+) S(−)De(+), Di(+) | Facial dysmorphism | Present study (2020) |

**FGFR3**
- **Gene**: *FGFR3*
- **Pathologic variant**: c.1537G>A (p.D513N)
- **Inheritance pattern**: AD
- **Phenotype**: Facial dysmorphism
- **Reference**: Rohmann et al. (2006)

**FGF10**
- **Gene**: *FGF10*
- **Pathologic variant**: c.409A>T (p.K137X)
- **Inheritance pattern**: AD
- **Phenotype**: Dolichocephaly, facial dysmorphism, micrognathia, eczematous dermatitis, toenail dysplasia
- **Reference**: Hajianpour et al. (2017)

**Abbreviations**: ?, not recorded; A, auricular; AD, autosomal dominant; De, dental; Di, digital; H, hearing; L, lacrimal; S, salivary.

For pathologic variants with many affected individuals, if at least one individual had the phenotype, it was recorded as positive.
Gyrata syndrome, Saethre–Chotzen syndrome, various cancers, and LADD syndrome (Lew, Bae, Rohmann, Wollnik, & Schlessinger, 2007).

Previous LADD syndrome reports have identified pathogenic FGFR2 variants which led to missense mutations in exon 16 and deletion mutations (Hajianpour et al., 2017; Rohmann et al., 2006). Our study reveals a novel variant in the first genetically analyzed Korean family with LADD syndrome. The proband and his father carried a single base substitution c.1547C>T (p.Ala516Val) in exon 11 of FGFR2 that resulted in a missense mutation inherited in an autosomal dominant pattern. Our study suggests that heterozygous FGFR2 c.1547C>T (p.Ala516Val) is a pathogenic variant.

LADD syndrome patients with FGFR2 mutations are characterized by lacrimal and salivary system abnormalities, auricular anomalies and hearing difficulties, dental and digital malformations, and variable facial dysmorphism and gastrointestinal involvement. Neither the proband nor his father in our study had associated facial dysmorphism or gastrointestinal symptoms.

Table 2 summarizes the genetically proven LADD syndromes in previous reports and our study. There were six proven pathologic variants for FGFR2, two for FGFR3, and four for FGF10. All the proven cases had dental and digital involvement. Three of the six variants of FGFR2 and both mutations of FGFR3 had no definite salivary gland involvement. In FGFR2 mutations, patients with deletion mutations had many anomalies in other organs compared to individuals with missense mutations. None of the patients with FGF10 mutations had hearing loss. Due to the small number of cases, it is difficult to prove a definite association between genotype and phenotype. There was also a range of phenotypes in families with the same genetic mutation, implying that additional factors influence the genotype to phenotype process.

The combination of xerostomia and xerophthalmia, seen in patients with LADD syndrome, can simulate Sjogren syndrome (Hajianpour et al., 2017) (Ostuni et al., 1995). While Sjogren syndrome is an immune disorder targeting tear glands and salivary glands, LADD syndrome is a genetic disorder causing dysgenesis or agenesis of the lacrimal duct/glands and salivary glands. The incidence or prevalence of pediatric Sjogren syndrome, especially in children because of the low prevalence rate of pediatric Sjogren, 0.098% to 3.6% (Petty et al., Textbook of Pediatric Rheumatology 7th edition).

When LADD syndrome is clinically suspected, sequencing and del/dup analysis of the three known genes associated with this condition may identify the pathogenic mutation. Otherwise, whole exome sequencing (WES) can be utilized when a clinical diagnosis of LADD syndrome is not made. WES can be used to diagnose patients with a suspected genetic condition who are not clinically diagnosed with a defined genetic syndrome. Utilizing genetic analysis such as WES may ascertain the affected gene for purposes of genetic counseling, identification of novel variants, decisions regarding therapy, and prevention of unnecessary treatment. In this case, we initially performed candidate sequencing of the proband’s FGF10. However, this targeted approach did not reveal a mutation in FGF10. With a strong clinical impression of LADD syndrome, we performed WES on the proband and identified a novel variant in FGFR2. This variant was verified by Sanger sequencing and revealed a heterozygous autosomal dominant inheritance pattern between father and son. In silico computational prediction analysis with Varsome marked it as likely pathogenic (Kopanos et al., 2019). WES may prove to be an important genetic diagnostic tool for patients with a suspected genetic condition who are not clinically diagnosed with a defined genetic syndrome.

4 CONCLUSION

We report the first LADD syndrome in a Korean family with a proven mutation. This novel, most likely pathogenic, variant in FGFR2: c.1547C>T (p.Ala516Val) may be used to identify patients with this genetic condition. For patients referred under the impression of Sjogren syndrome, rheumatologists are recommended to examine the patient for other anomalies carefully. If multiple systemic involvements are present, LADD syndrome should be considered as a possible diagnosis. WES may help identify patients with a suspected genetic condition who are not clinically diagnosed with a defined genetic syndrome. Computational prediction analysis tools may further assist validating novel genetic variants as pathogenic.

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