Clinical and genetic evaluations of Zimmermann-Laband syndrome with gingival fibromatosis: a rare case report

Yang Gu1,†, Xiaoxue Yang1,†, Xiaohoe Guo1, Meiling Wu1, Xiaoyao Huang1, Hao Guo1, Shijie Li1, Fei Fu1, Mingyuan Liu2, Kun Xuan1,*, Anqi Liu1,3,*

Abstract
Zimmermann-Laband Syndrome (ZLS; MIM 135500) is a rare genetic disorder with the main clinical manifestations of gingival fibromatosis and finger/toe nail hypoplasia. KCNH1 (potassium channel, voltage-gated, subfamily H, member-1), KCNN3 (potassium channel, voltage-gated, subfamily H, member-3) and ATP6V1B2 (ATPase H+ transporting V1 subunit B2) genes are considered causative genes for ZLS. However, there are limited reports about the diverse clinical presentation and genetic heterogeneity. Reporting more information on phenotype-genotype correlation and the treatment of ZLS is necessary. This case reported a 2-year-old patient with gingival enlargement that failure of eruption of the deciduous teeth and severe hypoplasia of nails. Based on a systemic examination and a review of the relevant literature, we made an initial clinical diagnosis of ZLS. A novel pathogenic variant in the KCNH1 gene was identified using whole-exome sequencing to substantiate our preliminary diagnosis. The histopathological results were consistent with gingival fibromatosis. Gingivectomy and gingivoplasty were performed under general anesthesia. After surgery, the gingival appearance improved significantly, and the masticatory function of the teeth was restored. After 2-year follow-up, the gingival showed slightly hyperplasia. Systemic examination and gene sequencing firstly contribute to provide information for an early diagnosis for ZLS, then timely removal of the hyperplastic gingival facilitates the establishment of a normal occlusal relationship and improves oral aesthetics.

Keywords
Zimmermann-Laband syndrome; Gingival fibromatosis; Gingivectomy; Case report

1. Introduction

Zimmermann-Laband Syndrome (ZLS; MIM 135500) is a rare disorder with varied clinical manifestations, and the characterized features are gingival hypertrophy, dysplasia or absence of the nails [1, 2]. Through searching in PubMed database, there are less than 60 literatures have reported ZLS. Studies reported several causative genes of ZLS, which encode potassium channels or vacuolar H+ -ATPase (Hydrogen-ion ATPases) (V-ATPase), including KCNH1 gene (MIM: 603305) [1, 3], ATP6V1B2 gene (MIM: 606939) [3], and KCNN3 gene (MIM: 602983) [4–6]. However, there is limited evidence about the relationship between mutation of causative genes and clinical features of ZLS. Investigating it will promote our understanding about the ZLS and provide more clinical information for further study about ZLS.

Gingival fibromatosis (GF) is characterized by diffuse fibrous connective tissue hyperplasia of gingival and it is a classical feature of the ZLS phenotype [2, 3, 7]. The excess gingival tissue can lead to functional difficulties, drifting of teeth, prolonged retention of primary dentition, poor plaque control and may also cause psychological and aesthetic problems [8].

Gingivectomy and gingivoplasty as symptomatic treatment for gingival fibromatosis achieve favorable clinical outcomes [9, 10]. However, the effect and long-term observation of gingivectomy for patients of ZLS exhibiting gingival fibromatosis remains unclear. Investigating it will provide more clinical experiences for ZLS.

At present, we are aware of only two Chinese cases with ZLS [11, 12], and neither was offered for genetic testing. This study reported the clinical, pathological and genetic evaluations of a child with Zimmermann-Laband syndrome, finding a novel mutation of causative gene KCNH1. Furthermore, after two-year follow-up, the present study shows timely removal of the hyperplastic gingival which is related to ZLS facilitates the oral health, providing more characteristics and treatment for ZLS.

2. Case presentation

A two-year-old boy was referred to School of Stomatology, Air Force Medical University for non-eruption of the upper teeth and gingival enlargement more than 1 year. He was the second son of a pair of healthy non-consanguineous couple and his brother was unaffected. Family and pregnancy history remains unclear. Investigating it will provide more clinical experiences for ZLS.

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1 Department of Preventive Dentistry, School of Stomatology, Air Force Medical University, State Key Laboratory of Military Stomatology & National Clinical Research Center for Oral Diseases & Shaanxi Clinical Research Center for Oral Diseases, 710032 Xi’an, Shaanxi, China
2 Department of Oral and Maxillofacial Surgery, Qinghai University Affiliated Hospital, 810000 Xining, Qinghai, China
3 Department of Stomatology, The 985 Hospital of PLA, 030001 Taiyuan, Shanxi, China

*Correspondence
xuankun@fmmu.edu.cn
(Kun Xuan);
xuankun@fmmu.edu.cn
(Anqi Liu)
† These authors contributed equally.

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was unremarkable. Anti-seizure drugs and/or cyclosporine had never been used by the patient or by his parents. Informed consent was written by his legal guardians.

Physical examination revealed that the proband had a bulbous soft nose, floppy ear, bilateral eyelid ptosis, thick lips that could not be held under the relaxed (Fig. 1A). He displayed hypoplastic distal phalanges of the thumb with limited extension and fingernail hypoplasia (Fig. 1B). His feet showed that hypoplasia of fingernails on toes 5, absence of nails on halluxes (Fig. 1C). The patient showed language and mental retardation, with clumsy gait.

Intraorally, both the free and attached gingiva showed diffuse, irregular hyperplasia and hypertrophy in the upper and lower deciduous dentition, which completely blocked the eruption of the maxillary teeth and covered almost the entire crowns of mandibular teeth. The gingival hyperplasia led to pseudo periodontal pockets, gingivitis and dental caries in mandibular primary molars (74, 75, 84) (Fig. 2A–C). Panoramic radiographic examination showed normal teeth for the child’s chronological age and no significant resorption of the alveolar bone (Fig. 2D).

Based on history and clinical features, the patient was preliminarily diagnosed as ZLS. To further explore the causative reasons, he was recommended to have a genetic test for definite diagnosis. Under the written consent of all participants, genomic DNA was extracted from the peripheral blood of the proband, his mother and brother. The proband’s father refused to test. Whole-exome sequencing (WES) was analyzed by the DIAN Diagnostics Corporation (Hangzhou, China). Sequence analysis revealed a novel heterozygous missense mutation—NM_172362.3: c.2198C>T; (p.Pro733Leu) of the KCNH1 gene on exon 11, which was not only in the proband, but also with his mother and brother. Silico tools (PolyPhen-2) predicted the mutation probably result in damaging and deleterious disease. Additionally, there was a de novo variant in the mutations—NM_015559. 3: c.370A>G (p.Ile124Val) of the SETBP1 gene only in the proband, which was also predicted to be probably damaging and deleterious disease (Fig. 3). The finding implied the mutation of KCNH1 gene putatively resulted in ZLS in this case. Combining extended interviews and WES results, we found that ZLS was segregated in his family in an autosomal—recessive manner and displayed a germline mutation.

Due to the increased gingival tissue affected chewing, appearance and pronunciation, we proposed surgical removal of the fibrous tissue under general anesthesia for the proband. The case study was conducted with the parents’ understanding and written consent to the intervention and research participation. Surgery firstly used round bur to remove the top enlargement gingival to determine the position of maxillary teeth. Then a successive, external bevel incision was made using a conventional scalpel to remove the hyperplastic gingival and expose primary dentition. At last, electrocautery was used to stop bleeding and trim gingival. Considering the proband had high caries risk, we removed carious tissue, filled with poly-acid modified composite resins and placed stainless steel crown (SSC) to protect the teeth (74, 75, 84) (Fig. 4A–C). The patient was advised to continue taking the antibiotic (amoxicillin, 20 mg/kg/d) for 3 days. A compound 0.2% chlorhexidine was prescribed for gargle twice a day for one week. At the same time, the parents were taught to brush the teeth for patient regularly, and oral hygiene was reinforced. The excised gingival tissue was sent for histopathological analysis. Haematoxylin-eosin (H&E) staining revealed the lesion consisted of dense or loose fibrous connective tissue arranged radially, mixed with the surrounding connective tissue, and the surface mucous squamous epithelium hyperplasia with elongated rete ridges extending into the underlying connective tissue, and lymphocytes, plasma cells could be seen below the epithelium results, which is consistent with gingival fibromatosis (Fig. 4D).

One month after surgery, gingival morphology of the whole mouth returned to normal, and the occlusal function and appearance were greatly improved (Fig. 5A,B). After 2 years, the intraoral examination showed that gingival hypertrophy recurred slightly in the maxillary incisor and mandibular molar areas, permanent lower left central incisor has been erupting and lower right central incisor is erupting (Fig. 5C–E). Panoramic radiographic examination detected nothing abnormal (Fig. 5F). The findings above exhibited gingivectomy for gingival hypertrophy of ZLS gained acceptable efficacy, through there was indispensable to oral health monitoring regularly.

3. Discussion

Zimmermann-Laband Syndrome (ZLS; MIM 135500) is a rare disorder characterized by gingival hypertrophy, dysplasia or absence of the nails, hypoplasia of the terminal phalanges of fingers and/toes, coarse facial features, intellectual disability of variable degree. It was first described by Zimmermann in 1928 in a 10-year-old mentally retarded girl and then Laband et al. [13] more fully delineated the disorder in a 38-year-old Trinidad woman and her 5 affected children. At present, ZLS have been reported in less than sixty literatures, and most patients are sporadic, though a few familial aggregations are observed with different inheritance patterns [2, 4, 14]. The clinical overlap of ZLS with several syndromes, including Dominant deafness-onychodystrophy syndrome (DDOD syndrome; MIM 124480) caused by haploinsufficiency of ATP6V1B2 [15], deafness-onychodystrophy-osteodystrophy-mental retardation-seizures syndrome (DOORS syndrome; MIM 220500) [16] caused by variants in TBC1D24 (TBC1 domain family member 24, MIM 613577) [16] and ATP6V1B2 [17], and Temple Baraitser syndrome (TMBTS, OMIM 611816) caused by mutations in KCNH1 [18]. Though the characteristics of ZLS are highly variable and phenotypic overlap with multiple syndromes, gingival hypertrophy and dysplasia of nails are core phenotypes which have been reported in most patients [2, 19]. In addition, more other variable features include epilepsy [20], cataract [21], hepatosplenomegaly [22], hypertrichosis [22, 23], mental retardation [22, 24], joint hyperextensibility [14, 22], deep plantar creases [25, 26], supernumerary teeth [27] have been presented. Given the variable features and causative genes from limited reports, it is a challenge to diagnose ZLS. Providing more information about clinical features and gene mutation may extend understanding of ZLS and be beneficial for early diagnosis.
FIGURE 1. Extraoral manifestations of the proband. Frontal view, bulbous soft nose, floppy ears, ptosis (A); Hand, hypoplastic distal phalanges of the thumbs, with limited extension and fingernail hypoplasia (B); Feet, hypoplasia of fingernails on right toes 5, aplasia of fingernails on hallux (C).

FIGURE 2. Oral manifestations of the proband. The frontal, lower arch and up occlusal view, which show diffuse overgrowth of the gingiva involving both the maxillary and mandibular arches (A–C); Panoramic radiograph showing normal teeth for the child’s chronological age (D).
**FIGURE 3. Genetic analysis of the family.** Sequencing chromatographs of genomic DNA reveals heterozygous missense mutations—c.2198C>T of the *KCNH1* (potassium channel, voltage-gated, subfamily H, member-1) gene in the proband, his mother and his brother. Mutations—c.370A>G of the *SETBP1* (SET binding protein 1) gene only in the proband.

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**FIGURE 4. Post-operative photo and pathological presentation.** Immediately after surgery, which show that full exposure of maxillary and mandibular dentition (A–C); Epithelium is thickened and displays narrow, elongated rete pegs that penetrate deep into the connective tissue (H&E staining, ×4) (D).
and treatment of ZLS. In the present case, the proband showed characterized hypoplastic nails, severe gingival fibromatosis which affected by the eruption of deciduous teeth, language and mental retardation.

*KCNH1* encodes the Eag1 (Kv10.1) channel, a member of the EAG (ether-à-go-go) family of voltage-gated K⁺ channels [28], and is expressed in diverse regions of the central nervous system [29]. It is recognized as an important regulator of cell proliferation in bone-marrow derived mesenchymal stem cells, and is involved in cell cycle control, proliferation and developmental processes [30, 31]. Functionally tested variants in *KCNH1* usually cause voltage-dependent displacement of activation to the left, thus increasing conductance K⁺ in the negative potential range [3]. Kortüm et al. [3] proposed that stabilization of the membrane potential in a more negative voltage range impedes opening of both voltage-gated Na⁺ and Ca²⁺ channels, which may explain the similarity of the gingival enlargement in ZLS-affected subjects to what is observed in some individuals treated with the Na⁺ channel blocker phenytoin or the Ca²⁺ channel blocker nifedipine. *KCNH1* hyperactivity due to activating mutations induces skeletal and nail malformations through altering signaling pathways involved in morphogenesis [32, 33]. *KCNH* channels are composed of four subunits, each subunit contains a voltage-sensor domain (transmembrane segments S1–S4), a pore domain (transmembrane segments S5–S6) and an intervening pore-forming, and a
Per-Arnt-Sim (PAS), domain in the amino-terminal region and a C-linker and cyclic-nucleotide-binding homology domain (CNBHD) in the C-terminal region [34]. Combining previously reported patients, suggesting domains S4–S6 are the hotspots for KCNH1-mutant disorders. However, in this study, the novel variant, c.2198C>T; (p.Pro733Leu), is located in the post—CNBHD of Kv10.1 in KCNH1, which has never been reported. Therefore, our results firstly found a novel missense mutation in KCNH1, providing more causative genetic information of ZLS, while further studies are required to understand the precise functional consequences of these alterations.

SETBP1 encodes the SET binding protein 1 expressed ubiquitously, but little is known about the function of SETBP1 [35]. De novo gain-of-function variants of SETBP1 are associated with Schinzel-Giedion midface retraction syndrome (MIM #269150), while haploinsufficiency of SETBP1 caused by loss-of-function (LoF) variant or a heterozygous gene deletion is related to Developmental Delay (DD), autosomal dominant 29 (MIM #616078) [36]. The observation of overgrown gingival tissues affecting the ability to speak has been reported in three previous patients with ZLS [21, 37]. In this case, we found a novel missense mutation in SETBP1, which was classified in some databases as possibly damaging speech and communication [38]. Although we have not found any reports about SETBP1 being associated with ZLS, the findings indicated the language retardation might be associated with SETBP1 mutation, providing a new putatively candidate gene for ZLS.

Gingival enlargement caused by several factors, such as inflammation, leukemia, drugs and inheritance. The most common forms of gingival enlargement are induced by systemic drugs, including the antiseizure drug phenytoin, the immunosuppressor cyclosporin and nifedipine, the calcium channel-blocker with antihypertensive activity [39]. Meanwhile, the condition may be related to hereditary factors and occurs as a non-syndromic hereditary gingival fibromatosis (HGF) or as a part of a syndrome [40, 41], such as namely amelogenesis imperfecta, juvenile hyaline fibromatosis, Zimmermann-Laband syndrome, Jones syndrome, Prune-Belly syndrome, Klippel-Trenaunay-Weber syndrome or Ramon syndrome [9]. We concluded that a detailed medical history and physical systemic evaluation is necessary for diagnosis of differentiate gingival fibromatosis, when occur developmental abnormalities in patients with gingival fibromatosis, we should be alert this may indicate the presence of rare diseases such as ZLS.

Treatment of GF depends on the severity of enlargement and whether there is any functional impact. Gingivectomy is the majority treatment, followed by gingivoplasty, electrocautery and carbon dioxide lasers [9, 10]. However, HGF is likely to recur with an overall recurrence rate of 34.92% after surgical treatment [9]. The recurrence rate is related to age, surgical technique and operation, location of hyperplasia and genetics [42]. In the case presented here, gingival enlargement had delayed the physiological process of tooth eruption, influenced pronunciation and masticatory of our patient, early surgery should be conducted. After surgery, the gingiva had an improved shape, and the patient’s chewing and lip closure had returned to normal. On the other hand, placing crowns on primary molar teeth with caries lesions or after pulp treatment may reduce the risk of major malfunctions or pain in the long run compared to fillings [43]. In high caries-risk children, definitive treatment of primary teeth with stainless steel crown (SSC) is better over time than multisurface intracoronal restorations [44, 45]. In this case, a good preventive effect has been achieved with no secondary caries and no periapical lesions two years after SSC placement. Thus, long-term follow-up after surgery is recommended and postoperative plaque control is necessary to maintain a normal gingival status and perform SSC can help improve dental management and care in children affected by early childhood caries.

4. Conclusions

This study reported the clinical and genetic information of a child with ZLS, providing a long-term follow-up of the comprehensive oral interventions of ZLS. In summary, a combination of medical history and systemic examination, supplemented by gene-related testing if necessary that is essential for achieving early diagnosis, correctly treatment and timely prevention for patients with ZLS. Maintaining treatment outcomes depends on the preservation of periodontal health and regular review.

ABBREVIATIONS

GF, Gingival fibromatosis; HGF, Hereditary gingival fibromatosis; ZLS, Zimmermann-Laband Syndrome; SSC, stainless steel crown; KCNH1, Potassium channel, voltage-gated, subfamily H, member-3; KCNN3, Potassium channel, voltage-gated, subfamily H, member-3; ATP6V1B2, ATPase H+-transporting V1 subunit B2; H+-ATPase, Hydrogen-ion ATPases; DDOD, Dominant deafness-onychodystrophy; DDORS, Deafness-onychodystrophy-osteodystrophy-mental retardation-seizures; TMCTS, Temple Baraitser syndrome; WES, Whole-exome sequencing; CNBHD, C-linker and cyclic-nucleotide-binding homology domain.

AVAILABILITY OF DATA AND MATERIALS

All data are available in the main text or the supporting information. The data used to support the findings of this study are available from the corresponding authors upon reasonable request.

AUTHOR CONTRIBUTIONS

YG and XXY—conceived and designed the report; collected data and writing-original draft. AQL—helped with manuscript preparation and revision. XHG, XYH and MYL—contributed to the medical examination and dental treatment of the patient; HG, MLW, SJL and FF—contributed to editorial changes in the manuscript. KX and AQL—conceived the concept, oversaw the collection of results, writing-review & edited the draft. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.
ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the institutional review board of the Air Force Medical University (KQ-YJ-2022-080). The informed consent was obtained from his parents for publication of this case report and any accompanying images.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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