Submitted: 15 October, 2022 Accepted: 05 December, 2022 Online Published: 03 March, 2023 DOI:10.22514/jocpd.2023.005

CASE REPORT

Journal of Clinical Pediatric Dentistry

Solitary median maxillary central incisor in Kabuki syndrome 2 with novel missense mutation of *KDM6A* and *ABCC8* genes

Farouk B. Rihani[1,*,†], May M. Altayeh[1,†], Rand Z. Al-Kilani[2,†], Rawan A. Alrejjal[1,†]

[1]Department of Pediatric Dentistry, Magic Tooth Dental Center, 11183 Jabal Amman, Amman, Jordan
[2]Dental Touch Clinic, 11821 Khalda, Amman, Jordan

***Correspondence**
fbrihani@yahoo.com
(Farouk B. Rihani)

[†] These authors contributed equally.

Abstract

Kabuki syndrome (KS) is an epigenetic machinery multisystem disorder with peculiar facial gestalt and dental-oral anomalies. This report describes the case of a KS patient with congenital hyperinsulinism, growth hormone deficiency and novel heterogenous missense mutations in exon 25 of the *KDM6A* (c.3715T>G, p.Trp1239Gly) and exon 1 of the *ABCC8* (c.94A>G, p.Asn32Asp) genes. She presented with solitary median maxillary central incisor (SMMCI) and mandibular incisor hypodontia, which could be a unique dental manifestation in KS 2.

Keywords

Hypodontia; Kabuki syndrome 2; *KDM6A*; Solitary central incisor

1. Introduction

Kabuki syndrome (KS) is a rare multisystem disorder initially described in Japan in 1981. It is reported to have a prevalence of 1 in 32,000–86,000 people [1, 2]. KS is characterized by distinctive dysmorphic facial features, minor skeletal abnormalities, visceral abnormalities, mild to moderate intellectual disability, postnatal growth deficiency, developmental delay, the persistence of fetal fingertip pads, and dental anomalies [3–5]. Dental anomalies commonly observed in KS patients include hypodontia (mainly affecting maxillary lateral incisors and mandibular incisors), oligodontia, microdontia, ectopic permanent first molars, screwdriver-shaped maxillary incisors, widely spaced teeth, and delayed tooth eruption [5, 6].

KS is caused by pathogenic variants in the *KMT2D* gene (KS 1, OMIM # 147920) on chromosome 12q13.12 with autosomal dominant inheritance, comprising 56%–76% of the affected patients, and the *KDM6A* gene (KS 2, OMIM # 300867) on chromosome Xp11.3 with X-linked dominant inheritance affecting 5%–8% of the patients [1, 3, 7]. Both genes have an interconnected epigenetic regulatory function in histone methylation, involving chromatin remodeling, and are essential regulators of muscle-specific genes during embryogenesis [3, 8].

In this report, we present the case of a KS 2 patient with maternally-inherited heterozygous novel missense mutations of *KDM6A* and *ABCC8* genes and an unusual dental anomaly of a solitary median maxillary central incisor (SMMCI) which has not been previously reported.

2. Case Report

The proband, a 7-year-old girl born to non-consanguineous parents, was referred to our pediatric dental clinic for dental treatment due to a lack of cooperative ability. Her family history included two brothers born with premaxillary natal teeth, one with neonatal death due to a congenital cardiac defect, and the other deceased one and a half months after birth due to gastrointestinal malformation. Our patient was born prematurely with a premaxillary supernumerary natal tooth at a gestational age of 34 weeks and weighed 1750 grams after a history of intrauterine growth restriction. Her supernumerary tooth exfoliated three months postnatally. However, due to failure to thrive and the presence of hypotonia, and neonatal jaundice, she was admitted to the newborn intensive care unit for ten days. At the age of 16 months, she had recurrent episodes of severe hypoglycemia and was diagnosed with growth hormone (GH) deficiency. At the age of two, laboratory examinations revealed that her serum glucose level was 23 mg/dL, GH level was 4 ng/mL and c-peptide level was 1.02 ng/mL. Subsequently, she was diagnosed with congenital hyperinsulinism and was unresponsive to diazoxide therapy. The patient was treated with recombinant human GH replacement therapy (Norditropin NordiFlex® 5 mg/1.5 mL), given as a daily 0.03 mg/kg subcutaneous injection.

Physical examination revealed that the patient had a moderate intellectual disability, a proportionate short stature, with a height of 102 cm (<3rd percentile), weighed 12.4 kg (<3rd percentile) and a head circumference of 44.5 cm (<3rd percentile). Craniofacially, she had large protruding ears, scanty thin scalp hair, high anterior hairline, laterally sparse eyebrows, long eyelashes, long palpebral fissures, bluish sclera, broad nasal tip, short nasal columella, slight maxillary retru-

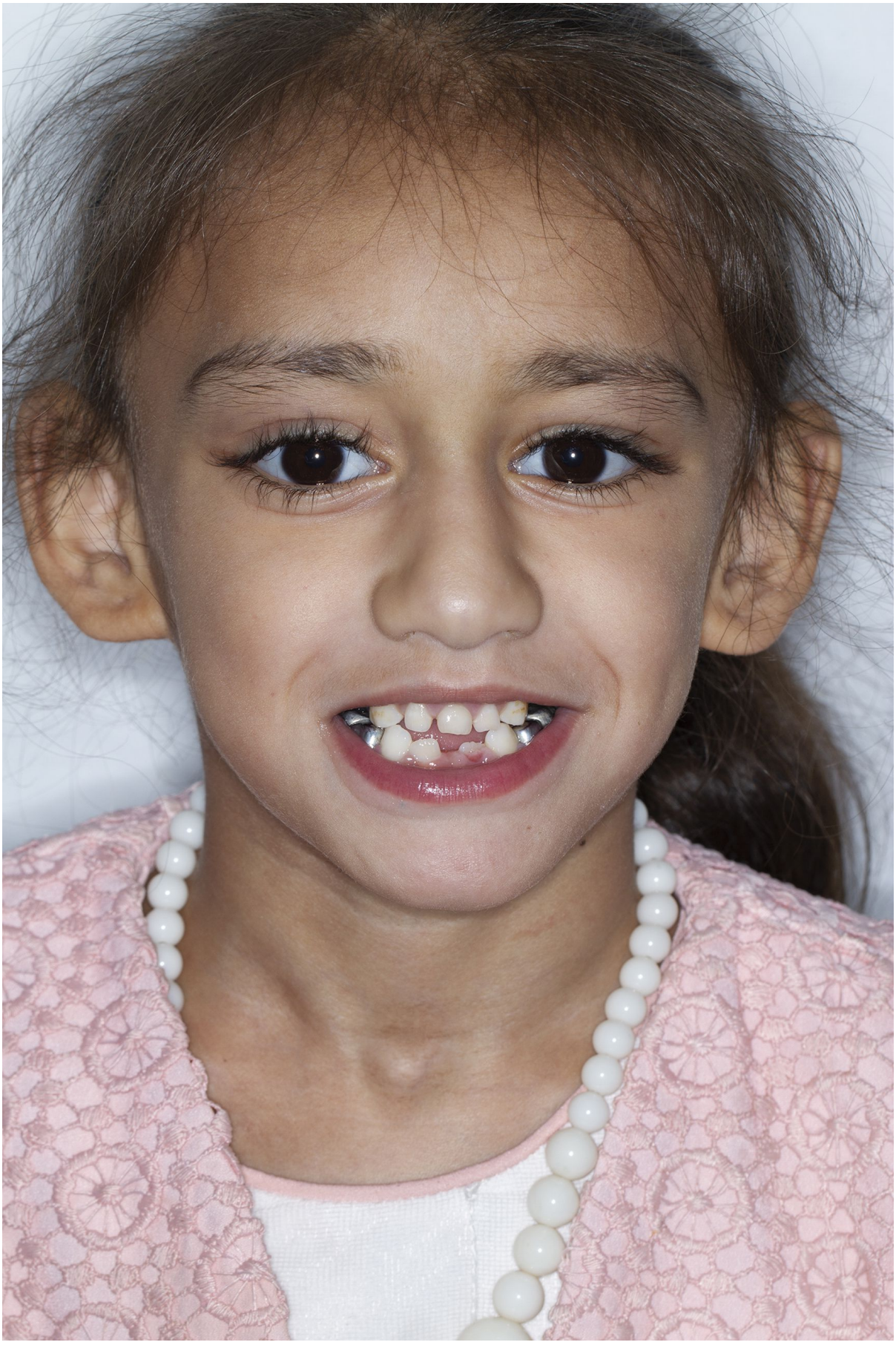

FIGURE 1. Frontal facial view with characteristic facial dysmorphism of the KS patient with protruding ears, bluish sclera, long eyelashes, sparse lateral eyebrows, and a primary solitary median maxillary central incisor.

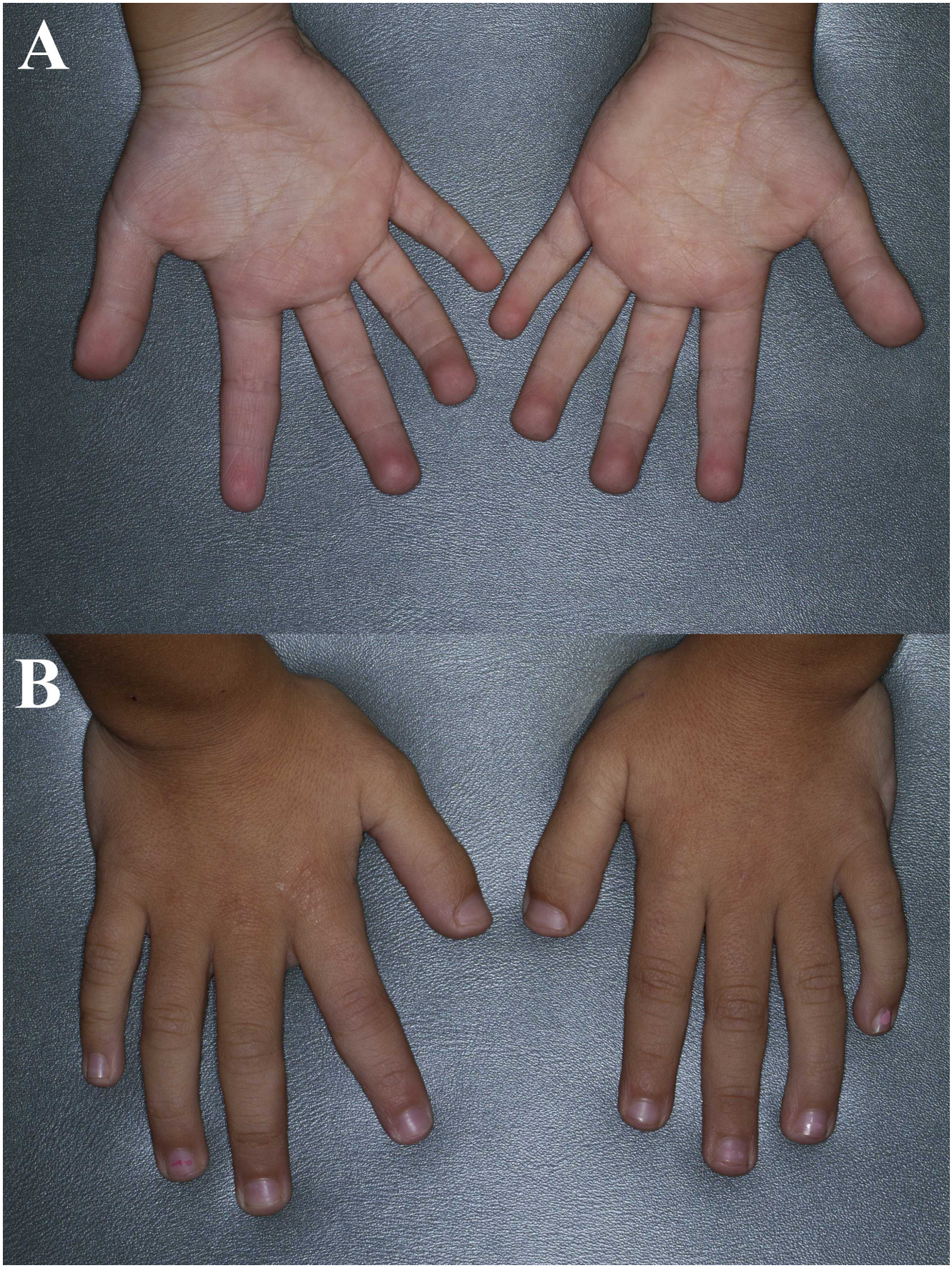

FIGURE 2. Hands View. (A) Palmar view of both hands demonstrating prominent digit pads. (B) Dorsal view of both hands showing broad thumbs, clinodactyly of the 5th fingers, and short fingernails.

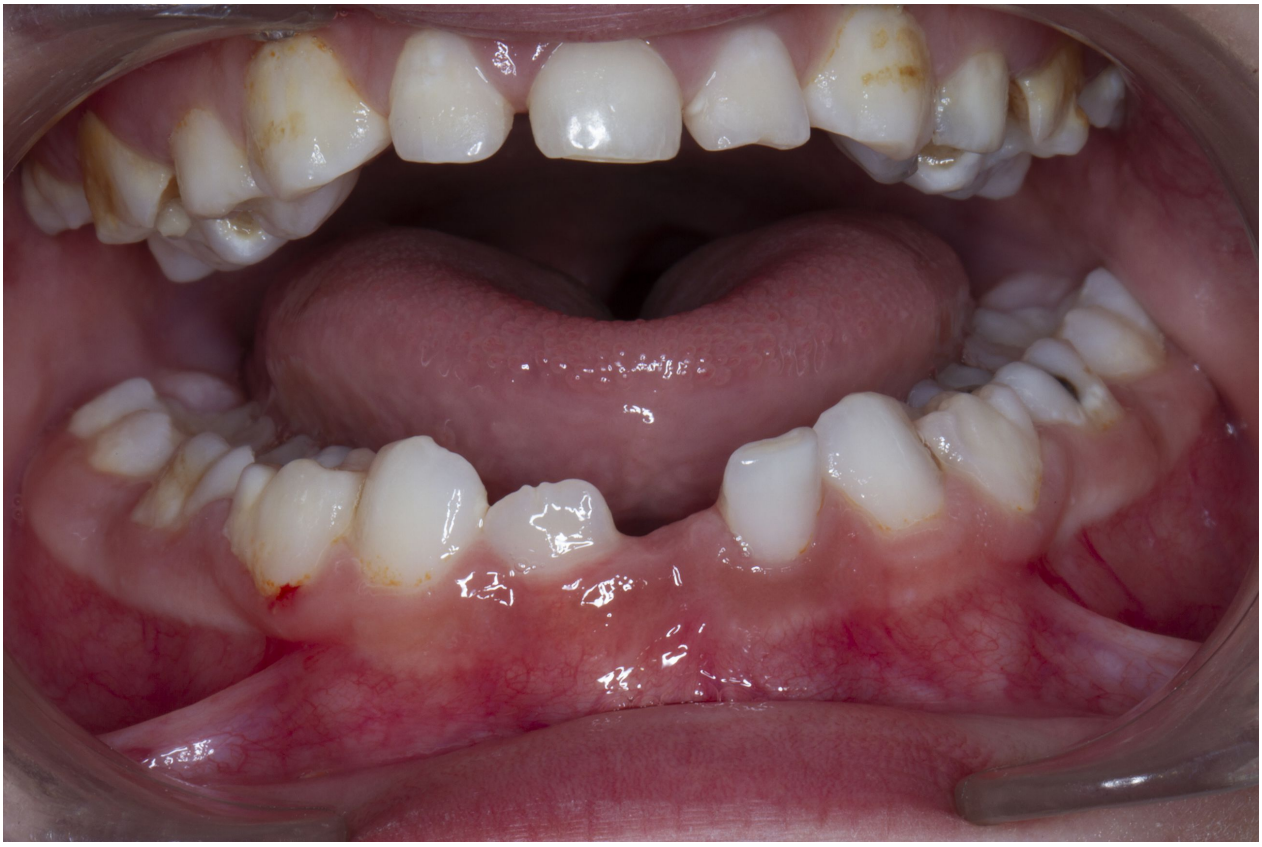

FIGURE 3. Intraoral frontal view of the maxillary and mandibular arches with the characteristic primary solitary median maxillary central incisor.

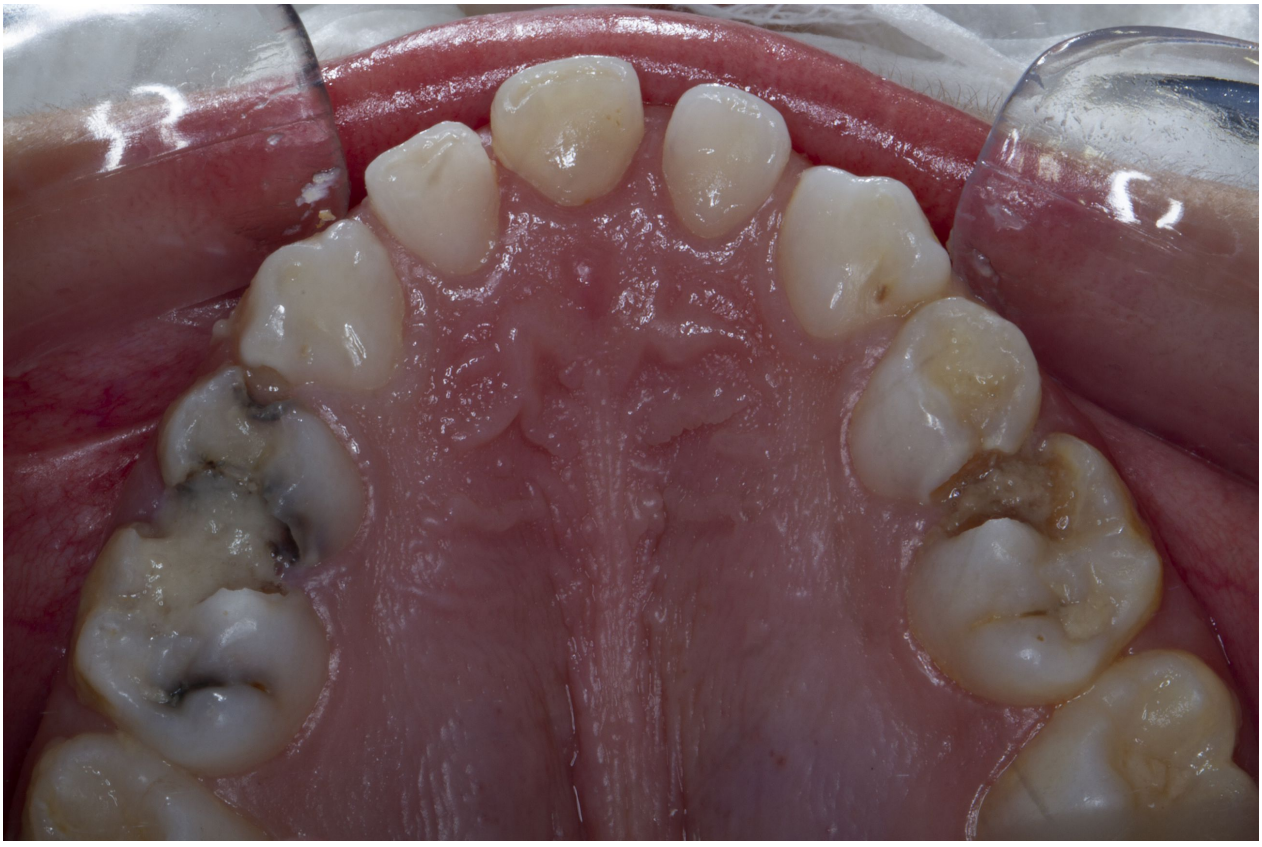

FIGURE 4. Intraoral occlusal view of the maxillary arch with a prominent median palatal raphe.

sion, thin upper lip, and full lower lip (Fig. 1). Additionally, her hands exhibited bilateral clinodactyly of the fifth fingers, broad thumbs with short fingernails, and prominent digit pads (Fig. 2).

Intraoral examination showed that the patient was in the early mixed dentition stage with two permanent mandibular incisors partially erupted, fully erupted first permanent molars, and a primary SMMCI (Fig. 3). The primary SMMCI and the primary mandibular left lateral incisor were of grade 2 (Grace and Smales Mobility Index). The labial surfaces of primary maxillary canines and second molars showed evidence of enamel hypoplasia. Her oral hygiene was deplorable, with multiple deep carious cavities, plaque, food debris deposits, and a plaque index of 2. Her labial gingiva exhibited mild gingival inflammation and a tendency to bleed on probing or gentle gingiva manipulation. Her primary molars demonstrated occlusal, deep proximal carious cavities, and interproximal gingival growth. In addition, her maxillary labial frenulum was absent, and the palate was narrow and high-arched, with a prominent median palatal raphe extending from the palatal rugae to the posterior border of the hard palate (Fig. 4). Periapical radiographs showed a succedaneous SMMCI and hypodontia of the permanent mandibular central incisors (Fig. 5).

Previous targeted next-generation sequencing of the coding regions and exon/intron boundaries of the pathogenic variants of 16 genes known to be implicated in congenital hyperinsulinism was performed on the DNA of the peripheral blood of the proband and both of her parents. This assay can also detect partial or whole gene deletions and duplications. The analysis showed the proband had a heterozygous novel X-linked missense mutation in exon 1 of the *ABCC8* gene (NM_001287174; c.94A>G, p.Asn32Asp), which she inherited from her unaffected mother, and the clinical significance of this variant is currently uncertain. Additionally, whole exome sequencing was performed on the DNA extracted from the peripheral blood of the proband and both parents, which also revealed a novel X-linked missense mutation in exon 25 of the *KDM6A* gene (NM_021140.2; c.3715T>G, p.Trp1239Gly) of the proband. Her mother was heterozygous for the p.Trp1239Gly variant in the *KDM6A* gene, and the clinical significance of this variant is also currently uncertain.

Due to the patient's intellectual disability and medical history, she underwent dental treatment under general anesthesia with constant serum glucose monitoring with continuous intravenous infusion of 10% dextrose and adhesive restorations on her primary maxillary canines and left primary mandibular canine. Fissure sealant was applied on all fissures of her permanent first molars, vital pulpotomy of the left primary mandibular first and second molars, and pulpectomy of the right primary mandibular first and second molars. Her first and second primary maxillary molars were extracted due to subgingival caries and extensive root resorption. All remaining primary molars were coronally restored with stainless steel crowns (Fig. 6).

3. Discussion

Hyperinsulinemic hypoglycemia (HH), insulin-dependent diabetes mellitus, congenital hypothyroidism, growth hormone deficiency and primary ovarian dysfunction are rare occurrences in KS patients [9]. Congenital HH occurs in 0.3%–4% of KS patients, of whom 50% have a pathogenic variant of the *KDM6A* gene [10]. Furthermore, pathogenic variants of the *ABCC8* and *KCNJ11* genes are the most frequently involved genes with HH and encode for the two subunits of the ATP-sensitive potassium channel of pancreatic β-cells that regulate insulin secretion [10, 11]. Moreover, 50% of SMMCI patients have a short stature, with many demonstrating growth hormone deficiency [12]. Comparatively, our patient had heterogenous nonsense mutations of the *KDM6A* and *ABCC8* genes, which are classified as variants of uncertain significance presented with HH, growth hormone deficiency and short stature.

Endocrine abnormalities in KS can affect dental treatment planning as KS patients are more susceptible to episodes of hypoglycemia and hyperglycemia [9]. Moreover, they have increased susceptibility to infections due to hypogammaglobulinemia, causing upper respiratory tract infections, pneumonia and recurrent otitis media, which is further exacerbated by the presence of cleft palate and Eustachian tube anomalies, rendering them an absolute contraindication for dental treatment under nitrous oxide/oxygen inhalation [9, 13, 14]. Also, congenital cardiac defects can be seen in 42% to 80% of KS patients, making them susceptible to infective endocarditis after dental surgical procedures, and thus preoperative antibiotic prophylaxis is mandatory [13, 15]. Other systemic abnormalities in KS patients that can negatively affect dental management include seizures, cognitive difficulties, autoimmune hemolytic anemia, immune thrombocytopenic purpura, renal malformations, and hepatobiliary disorders [9, 13]. Our patient suffered from hypoglycemia episodes, which required constant serum glucose monitoring and intravenous dextrose infusion to prevent any medical complications.

Dental-oral anomalies are common in KS patients, affecting 60% to 86% of them (Table 1) [5, 6, 13, 16–20]. The maxillary lateral and mandibular central incisors are the most commonly missing teeth in KS patients and probably more common in KS patients with a heterozygous pathogenic variant of the *KMT2D* gene [5, 6, 8, 17, 19, 20]. Oligodontia, hypodontia, screwdriver-shaped incisors, ectopic permanent first molars, cleft palate, and lip pits are considered supportive features in the clinical diagnosis of KS [5]. On the other hand, SMMCI is associated with dental-oral abnormalities, including narrow/V-shaped palate, prominent median palatal raphe, absent maxillary labial frenulum, absent incisive papilla, indistinct philtrum, and arch-shaped upper lip. Approximately 82% of patients with permanent SMMCI present with a primary SMMCI. Furthermore, SMMCI can be associated with the deletion of chromosome 7 at 7q36.1 and chromosome 18 at 18p11.3, del(22q11.2), 47XXX syndrome, CHARGE syndrome, VACTERL association, Duane retraction syndrome, ectodermal dysplasia and holoprosencephaly [12, 21]. Our patient showed dental anomalies in KS and palatal anomalies in SMMCI. Many cases of primary dentition with SMMCI are not treated. In permanent dentition, orthodontic space can be created by maxillary expansion and/or maxillary premolar extraction to create a space for another permanent maxillary central incisor. In other situations, extraction of the permanent SMMCI orthodontic alignment of the permanent maxillary

TABLE 1. Dental and Oral Features in Patients with Kabuki Syndrome.

Dental
Hypodontia/oligodotia*†
Microdontia/conical teeth*
Screwdriver-shaped incisors*
Widely spaced teeth/median diastema*†
Supernumerary teeth
Ectopic permanent first molars*
Fusion/gemination
Delayed tooth eruption*
Retained teeth*
Submerged primary teeth
Impacted teeth*
Enamel hypoplasia†
Large pulp chamber/taurodontic first permanent molars*
External root resorption of the permanent maxillary incisors and molars*
Abnormal root resorption/short roots and/or unusual root development†
Pulpal hard tissue deposition of the permanent molars
Tooth transposition
Natal/neonatal teeth*†
Talon cusp
Solitary median maxillary central incisor†
Palate and uvula
High-arched palate*†
V-shaped maxillary arch
Cleft lip/palate*
Sub-mucosal cleft palate
Soft palate paralysis
Bifid uvula*
Long uvula
Prominent median palatal raphe†
Tongue
Bifid tongue*
Macroglossia
Tongue thrust
Lips and frenula
Lower lip pits/fistulae
Paramedian elevation on the lower lip/lip nodules
Thin vermillion of the upper lip*†
Thick/full lower lip*†
Tent-shaped mouth
Absent maxillary labial frenulum†
Orthodontic
Malocclusion/crowded teeth*
Anterior open bite
Deep bite
Small dental arch*

TABLE 1. Continued.

Dental
Maxillary recession*†
Mid-facial hypoplasia*
Mandibular protraction†
Micrognathia*
Posterior crossbite*

**, commonly observed in Kabuki syndrome cases; †, found in our present case.*

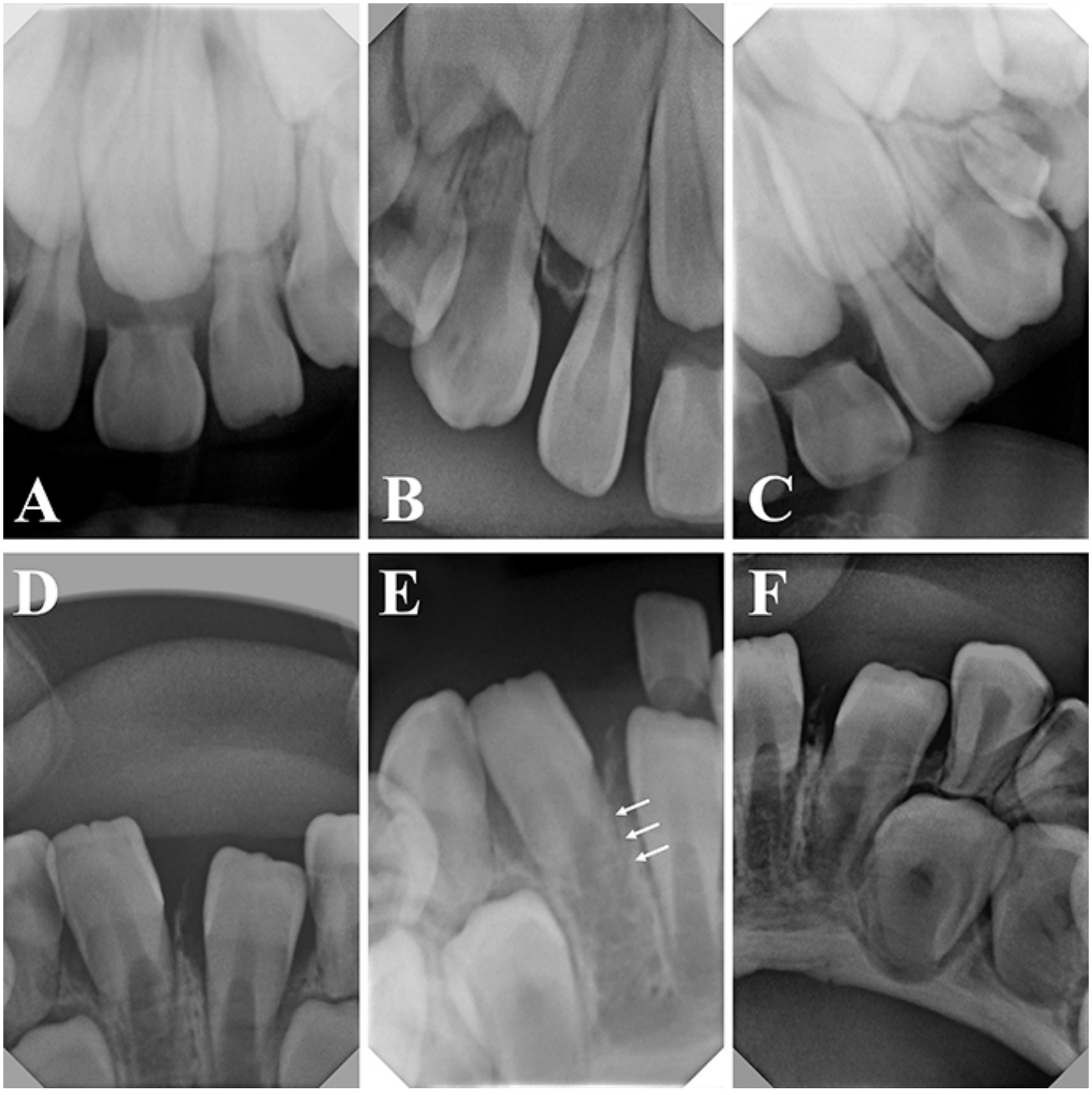

FIGURE 5. Anterior Periapical Radiographs. (A–C) Periapical radiographs of the anterior maxillary area. (A) A rootless primary solitary median maxillary central incisor (SMMCI) and succedaneous permanent SMMCI. (B) Right maxillary lateral incisor area. (C) Left maxillary lateral incisor area. (D–F) Periapical radiographs of the mandibular anterior area. (D) Hypodontia of the permanent mandibular central incisors and presence of the permanent mandibular lateral incisors with delayed root development (white arrows). (E) Right mandibular lateral incisor area. (F) Left mandibular lateral incisor area. Figs. 5D and 5F were taken after the exfoliation of tooth number 72.

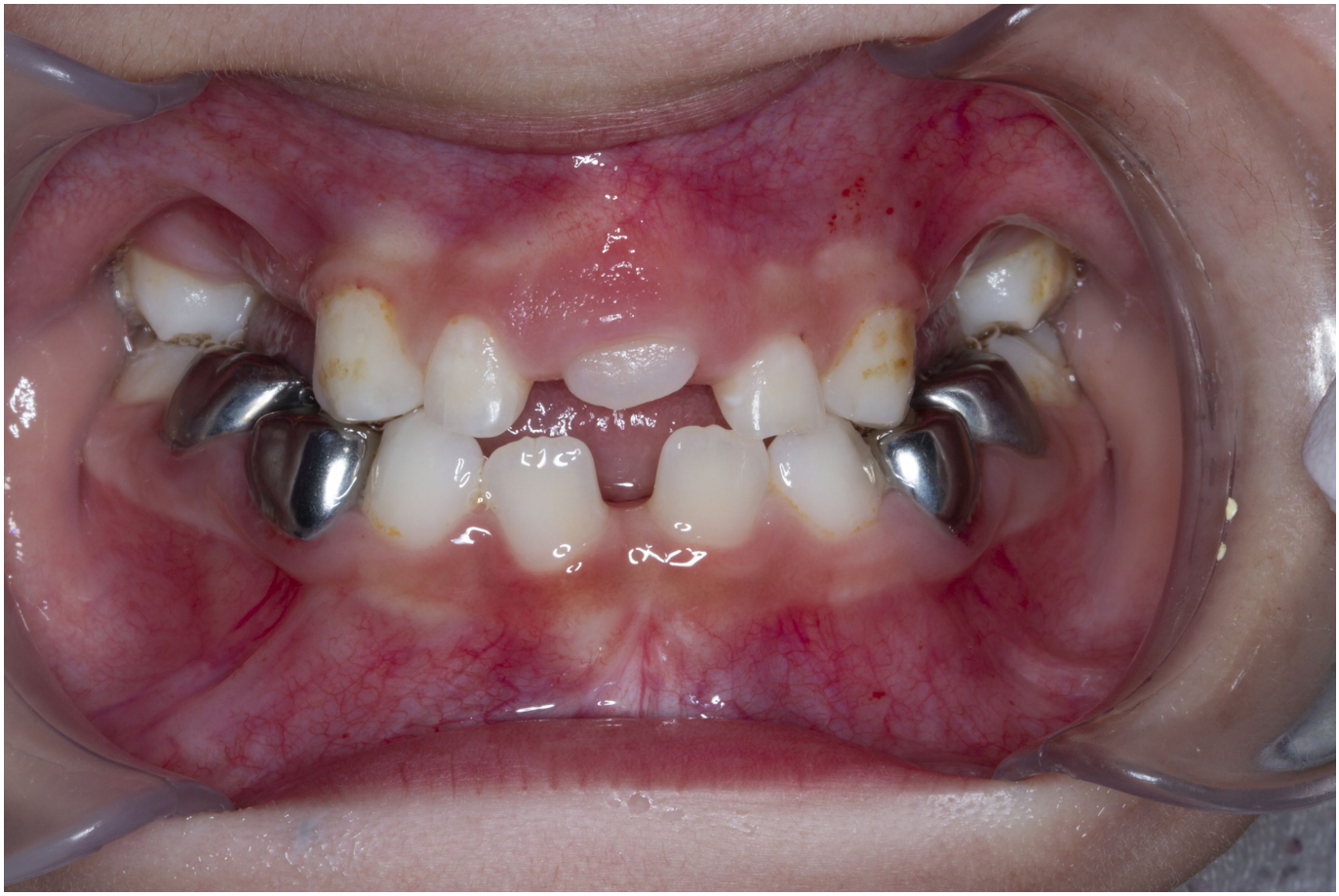

FIGURE 6. Intraoral frontal view four months after treatment showing a partially erupted permanent solitary median maxillary central incisor and fully erupted permanent mandibular lateral incisors.

lateral incisors combined with crown reshaping can replace the permanent maxillary central incisors [21–23]. The lack of cognitive abilities in our patient might hinder her cooperation in future orthodontic treatment.

4. Conclusion

SMMCI is a striking dental anomaly that cannot be easily missed clinically due to its prominent anterior positioning and associated palatal anomalies. Therefore, for cases presenting with SMMCI and associated dysmorphic facial features, KS should be considered in the differential diagnosis. Clinical awareness of associated systemic disorders of KS needs to be emphasized as they can affect dental treatment planning.

ABBREVIATIONS

SMMCI: solitary median maxillary central incisor; KS: Kabuki syndrome; GH: growth hormone; HH: hyperinsulinemic hypoglycemia.

AVAILABILITY OF DATA AND MATERIALS

The data presented in this case report is available at reasonable request from the corresponding author.

AUTHOR CONTRIBUTIONS

FR—diagnosed the case, prepared the references, and wrote the discussion. MA—treated the case and wrote the case presentation. RZA—formulated the treatment plan and wrote the abstract. RAA—treated the case and wrote the abstract. All authors approved the final version of the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Written consent form has been acquired from the parent.

ACKNOWLEDGMENT

Not applicable.

FUNDING

This research received no external funding.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

[1] Miyake N, Koshimizu E, Okamoto N, Mizuno S, Ogata T, Nagai T, *et al*. MLL2 and KDM6A mutations in patients with Kabuki syndrome. American Journal of Medical Genetics Part A. 2013; 161A: 2234–2243.

[2] White SM, Thompson EM, Kidd A, Savarirayan R, Turner A, Amor D, *et al*. Growth, behavior, and clinical findings in 27 patients with Kabuki (Niikawa-Kuroki) syndrome. American Journal of Medical Genetics Part A. 2004; 127A: 118–127.

[3] Lederer D, Grisart B, Digilio MC, Benoit V, Crespin M, Ghariani SC, *et al*. Deletion of KDM6a, a histone demethylase interacting with MLL2, in three patients with kabuki syndrome. The American Journal of Human Genetics. 2012; 90: 119–124.

[4] Schrander-Stumpel C, Meinecke P, Wilson G, Gillessen-Kaesbach G, Tinschert S, König R, *et al*. The Kabuki (Niikawa-Kuroki) syndrome: further delineation of the phenotype in 29 non-Japanese patients. European Journal of Pediatrics. 1994; 153: 438–445.

[5] Adam MP, Banka S, Bjornsson HT, Bodamer O, Chudley AE, Harris J, *et al*. Kabuki syndrome: international consensus diagnostic criteria. Journal of Medical Genetics. 2019; 56: 89–95.

[6] Teixeira CS, Silva CRL, Honjo RS, Bertola DR, Albano LMJ, Kim CA. Dental evaluation of Kabuki syndrome patients. The Cleft Palate Craniofacial Journal. 2009; 46: 668–673.

[7] Bögershausen N, Gatinois V, Riehmer V, Kayserili H, Becker J, Thoenes M, *et al*. Mutation update for Kabuki syndrome genes KMT2D and KDM6A and further delineation of X-linked Kabuki syndrome subtype 2. Human Mutation. 2016; 37: 847–864.

[8] Micale L, Augello B, Maffeo C, Selicorni A, Zucchetti F, Fusco C, *et al*. Molecular analysis, pathogenic mechanisms, and readthrough therapy on a large cohort of Kabuki syndrome patients. Human Mutation. 2014; 35: 841–850.

[9] Adam MP, Hudgins L. Kabuki syndrome: a review. Clinical Genetics. 2005; 67: 209–219.

[10] Hoermann H, El-Rifai O, Schebek M, Lodefalk M, Brusgaard K, Bachmann N, *et al*. Comparative meta-analysis of Kabuki syndrome with and without hyperinsulinaemic hypoglycaemia. Clinical Endocrinology. 2020; 93: 346–354.

[11] Yap KL, Johnson AEK, Fischer D, Kandikatla P, Deml J, Nelakuditi V, *et al*. Congenital hyperinsulinism as the presenting feature of Kabuki syndrome: clinical and molecular characterization of 10 affected individuals. Genetics in Medicine. 2019; 21: 233–242.

[12] Kjaer I, Balslev-Olesen M. The primary maxillary central incisor in the solitary median maxillary central incisor syndrome. European Journal of Paediatric Dentistry. 2012; 13: 73–75.

[13] Rocha CT, Peixoto ITA, Fernandes PM, Torres CP, de Queiroz AM. Dental findings in Kabuki make-up syndrome: a case report. Special Care in Dentistry. 2008; 28: 53–57.

[14] American Academy of Pediatric Dentistry. Use of nitrous oxide for pediatric dental patients. The Reference Manual of Pediatric Dentistry. American Academy of Pediatric Dentistry. 2021; 338–343.

[15] Digilio MC, Gnazzo M, Lepri F, Dentici ML, Pisaneschi E, Baban A, *et al*. Congenital heart defects in molecularly proven Kabuki syndrome patients. American Journal of Medical Genetics Part A. 2017; 173: 2912–2922.

[16] Petzold D, Kratzsch E, Opitz Ch, Tinschert S. The Kabuki syndrome: four patients with oral abnormalities. European Journal of Orthodontics. 2003; 25: 13–19.

[17] Santos CN, Cardoso MCAC, Turrioni AP, Santo ASM, Paranhos LR. Talon cusp in the temporary dentition of a patient with Kabuki syndrome: Case report with a two-year follow-up. Special Care in Dentistry. 2019; 39: 624–630.

[18] Matsune K, Shimizu T, Tohma T, Asada Y, Ohashi H, Maeda T. Craniofacial and dental characteristics of Kabuki syndrome. American Journal of Medical Genetics. 2001; 98: 185–190.

[19] Santos BMD, Ribeiro RR, Stuani AS, Silva FWGDPE, Queiroz AMD. Kabuki make-up (Niikawa-Kuroki) syndrome: dental and craniofacial findings in a Brazilian child. Brazilian Dental Journal. 2006; 17: 249–254.

[20] Takada K, Fukushima H, Watanabe S, Ishida M, Ogasawara H, Motokawa W. Occlusal guidance of two Kabuki make-up syndrome patients: case reports. Journal of Clinical Pediatric Dentistry. 2005; 28: 113–118.

[21] Hall RK. Solitary median maxillary central incisor (SMMCI) syndrome. Orphanet Journal of Rare Diseases. 2006; 1: 12.

[22] Schneider UEM, Moser L. Orthodontic space closure in a young female patient with solitary median maxillary central incisor syndrome. American Journal of Orthodontics and Dentofacial Orthopedics. 2021; 160: 132–146.

[23] Sekerci AE, Ucar FI, Gumus H, Aydinbelge M, Sisman Y. Solitary median maxillary central incisor: a report of 2 cases. Pediatric Dentistry. 2012; 34: 150–155.

How to cite this article: Farouk B. Rihani, May M. Altayeh, Rand Z. Al-Kilani, Rawan A. Alrejjal. Solitary median maxillary central incisor in Kabuki syndrome 2 with novel missense mutation of *KDM6A* and *ABCC8* genes. Journal of Clinical Pediatric Dentistry. 2023; 47(2): 108-116. doi: 10.22514/jocpd.2023.005.