Cranio-Oro-Facial Characteristics of Two Thai Patients with Apert Syndrome

Yanisa Wongbanthit[1, 5], Wuttichart Kamolvisit[2, 3], Preeya Suwanwitid[4], and Thantrira Porntaveetus[*, 5]

[1]Master of Science Program in Geriatric Dentistry and Special patient care, Faculty of Dentistry, Chulalongkorn University, Bangkok, Thailand
[2]Center of Excellence for Medical Genomics, Medical Genomics Cluster, Department of Pediatrics, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand
[3]Excellence Center for Genomics and Precision Medicine, King Chulalongkorn Memorial Hospital, the Thai Red Cross Society, Bangkok, Thailand
[4]Department of Orthodontics, Faculty of Dentistry, Chulalongkorn University, Bangkok, Thailand
[5]Genomics and Precision Dentistry Research Unit, Department of Physiology, Faculty of Dentistry, Chulalongkorn University, Bangkok, Thailand
[*]Corresponding author. E-mail: thantrira.p@chula.ac.th

Abstract

Apert syndrome is a rare congenital abnormality characterized by the fusion of multiple cranial sutures (craniosynostosis) and distinctive malformations of the skull, face, hands, feet, and dentition. Variations in the fibroblast growth factor receptor 2 (FGFR-2) gene are the cause of Apert syndrome. Currently, there is still a gap in knowledge about oro-dental features in patients with Apert syndrome. This study aimed to characterize Cranio-oro-facial manifestation and identify genetic variations related to Apert syndrome in Thai patients. Two Thai patients with Apert syndrome receiving treatment at the Princess Sirindhorn Craniofacial Center (PSC center) at King Chulalongkorn Memorial Hospital were recruited. Medical and dental records were obtained. Physical and oral manifestations, oral hygiene (OHI-S) and caries status (DMFT, dmft, DMFS, dmfs), occlusion, and maxillomandibular relationship were investigated. Pathogenic variants associated with Apert were identified by Sanger sequencing. Patient-1 and Patient-2 showed typical Apert features including craniosynostosis, hand syndactyly, and dysmorphic facial features. Cephalometric analysis revealed that the patients had retrognathic maxilla, proclined upper incisors, retroclined lower incisors, and protruded lower lip. Compared with general Thai children of the same sex and age, the patients had higher caries prevalence and caries risk score assessment. Sanger sequencing identified that both patients had hot-spot FGFR2 variants. Patient-1 possessed the heterozygous missense variant, c.755C>G (p.Ser252Trp) and Patient-2 harbored the heterozygous missense variant, c.758C>G (p.Pro253Arg). The identified pathogenic FGFR2 variants corresponding with patients' phenotypes indicate that both patients were affected with Apert syndrome. The patients with Apert syndrome exhibit multiple Cranio-oro-facial anomalies. With poor oral hygiene and high caries risk, our study suggests that a multidisciplinary team is essential to deliver prompt management of Cranio-oro-facial abnormalities in patients with Apert syndrome. Vigilant dental check-ups and oral hygiene care must be implemented for the patients.

Keywords**:** *Craniosysnosotis, Dental caries, Malocclusion, Fibroblast growth factor*

1. Introduction

"Apert Syndrome (AS)," introduced by Apert, the French physician, in 1906 (Apert, 1906) is an autosomal-dominant inherited disease, also known as Acrocephalosyndactyly type I. The incidence of AS is approximately 15 in 1,000,000 live births (Jose et al., 2021) or 4% of craniosynostosis cases (Cohen, Jr, and Kreiborg, 1992). AS is characterized by premature fusion of one or more skull sutures, predominantly coronal sutures, ocular proptosis, mid-facial hypoplasia, severe dental crowding, missing teeth, enamel hypoplasia, a fusion of cervical vertebrae (mostly C5-C6), and symmetry syndactyly of hands and feet (Kobayashi et al., 2021). Impaired cognitive and learning skills are also present in some cases (Lopez-Estudillo et al., 2017). Several techniques have been introduced to manage cranial distortion in AS patients including linear craniectomy and fragmentation of the cranial vault (Thanapaisal, Chowchuen B, and Chowchuen P, (2010); Bir et al., (2014)), fronto-orbital advancement to improve bilateral coronal synostosis (Cohen et al., 1991), and endoscopic suturectomy (Kajdic, Spazzapan, and Velnar, 2018). The

goal of surgical reconstructions is to create optimal space for brain growth, correct neurological damages, and prevent visual-respiratory problems. Therefore, medical records, oral examination reports, and also craniofacial profiling including lateral cephalometric analysis of AS patients are necessary for manipulating an appropriate treatment plan for the patient.

Genetic causes of AS are the missense variants in the fibroblast growth factor receptor-2 (FGFR-2) gene. In almost all reported cases, AS has been caused by one of two specific variants in the *FGFR2* gene: the c.755C>G (p.Ser252Trp) found in about 85% of cases and c.758C>G (p.Pro253Arg) in about 15% of cases (Wilkie et al., 1995). The FGFR2 is the receptor in the FGF pathway that plays a major role in controlling the homeostasis and proliferation of various cells. Alteration in the FGF pathway leads to abnormal cranial vault development and skeletal disorders, resulting in elevated intracranial pressure, brain damage, and irregular function of internal organs (Moosa, and Wollnik, 2016). The standard and simple method to detect genetic variants associated with AS is the Sanger sequencing, which is the DNA sequencing based on the selective incorporation of chain-terminating dideoxynucleotides by DNA polymerase during in vitro DNA replication (Sanger, Nicklen, and Coulson, 1977).

Although many AS cases have been reported, there are still limited reports about oral hygiene conditions and cephalometric tracing in AS patients, together with their medical condition and genetic variants.

2. Objectives

The aims of this study are therefore to gather and characterize Cranio-oro-facial features, and pathogenic variants related to Apert syndrome in Two Thai patients.

3. Materials and Methods

3.1 Patient selection and ethical consideration

Patients with complete medical records and radiographic data were selected for this study. Two patients with Apert Syndrome receiving treatment at the Princess Sirindhorn Craniofacial (PSC) Center at King Chulalongkorn Memorial Hospital were enrolled. This study was approved by the Institutional Review Board, Faculty of Medicine, Chulalongkorn University, Thailand (COA no. 1348/2021). Inform consents were obtained from the participants and their legal guardians.

3.2 Cranio-oro-facial data

An oral examination was performed by an experienced dentist (Y.W.). A simplified Oral Hygiene Index (OHI-S) was used to assess the oral health status of the patient (Greene, and Vermillion, (1964); Amira, Fauziah, and Suharsini, (2019)). The caries prevalence comprising the Decayed, Missing, and Filled Teeth index (DMFT/dmft) and the Decayed, Missing, and Filled Surfaces index (DMFS/dmfs) was recorded. Caries risk assessment and maxillomandibular relationship (Angle's classification) were evaluated. Lateral Cephalogram tracing was analyzed by an experienced orthodontist. Tooth number was used according to The Federation Dentaire Internationale (FDI) Numbering System.

3.3 Genetic analysis

DNA was extracted from peripheral blood according to a previous study (Intarak et al., 2021). Primers that specifically amplified the FGFR2 gene were used in a polymerase chain reaction. The PCR product was then examined for the pathogenic variants associated with Apert syndrome by Sanger sequencing.

4. Results and Discussion

4.1 Results

Patient-1 was a 7-year-old girl. At the age of 9 months, the patient had complex syndactyly on both hands-feet, abnormal head contour, and craniosynostosis. Examinations at 7 years old revealed hypertelorism, exorbitism, cleft palate, and midface hypoplasia (Figure 1A, B). She had undergone multiple

operations including fronto-orbital advancement (FOA) surgery at 1 year old, tonsillectomy with myringotomy at 2 years old, hand webspace separation at 9 months and 3 years old, and palatoplasty at 7 years old. She also had severe stage obstructive sleep apnea (OSA) requiring continuous positive airway pressure (CPAP) machine. The parents and other family members were healthy.

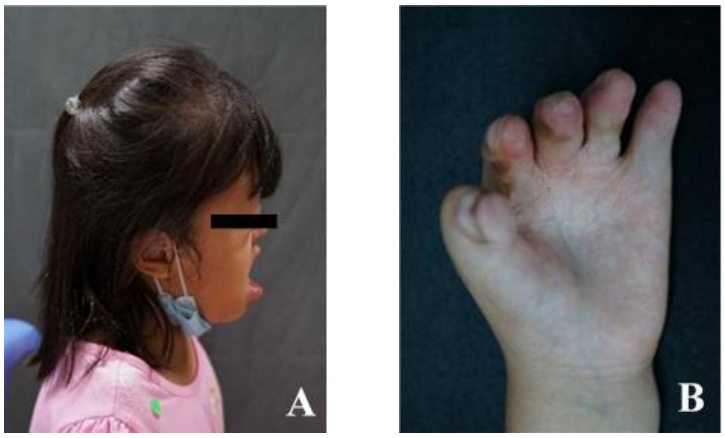

Figure 1 Images of Patient-1 at 7 years old. Lateral profiles showed maxillary hypoplasia and lower lip protrusion (A) The patient's left hand after receiving surgical separation (B)

Patient-2 was a 12-year-old boy. Physical examination showed bilateral coronal synostosis, hypertelorism, downslanting palpebral fissures, exorbitism, mid-facial hypoplasia, cleft palate, bilateral syndactyly of hands and feet, hearing loss, and obstructive sleep apnea (Figure 2). At 7 years old, he developed bilateral otitis media with effusion (OME), adenotonsillar hypertrophy, mild OSA, and acquired subglottic stenosis. The patient underwent several surgeries including fronto-orbital advancement, left and right ear myringotomy with Pressure Equalizer (PE) tube, and separation of left and right-hand webspace. He had low average intelligence (IQ score 81) and required psychological support. The parents and other family members were healthy.

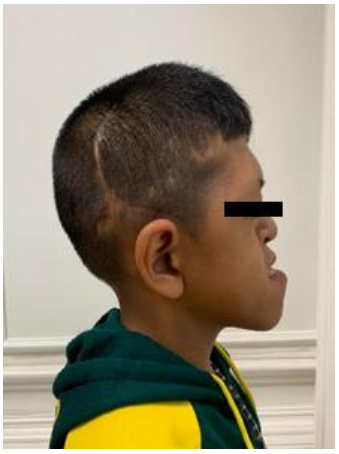

Figure 2 Image of Patient-2 at 12 years old. Lateral profiles showed midface hypoplasia and lower lip protrusion

Oro-dental manifestations

Patient-1, in the mixed dentition, had severe malocclusion, Class III Angle's classification, multiple dental caries, gingival inflammation, generalized heavy plaque, food debris deposition, and poor oral hygiene. The OHI-S score was 2.67 (classified as fair oral status). The dmft score was 13 and dmfs was

29, indicating that the patient's primary teeth had high caries prevalence. The teeth 55, 54, 62, 64, and 75 developed asymptomatic irreversible pulpitis and were required pulpal treatment or extraction. The DMFT and DMFS scores were zero, indicating that the permanent teeth had low caries prevalence. Caries risk assessment revealed a high risk of caries.

Patient-2, in the mixed dentition, had Class III malocclusion, severe maxillary teeth crowding, generalized moderate plaque deposition, minimal calculus deposits, gingival inflammation, and poor oral hygiene. The DMFT and DMFS scores were 9 and 15 respectively, indicating high caries prevalence in the permanent teeth. The permanent lower left first molar developed pulp necrosis and severely deteriorated, causing tooth pain. The dmft score was 1 and dmfs score was 2, respectively (The lower right first molar was the only primary tooth left). The patient had a history of multiple teeth extraction due to dental decay. The patient had an OHI-S score of 1.33. The caries risk assessment was high. Intraoral manifestations of Patient-1 and Patient-2 are shown in Table 1.

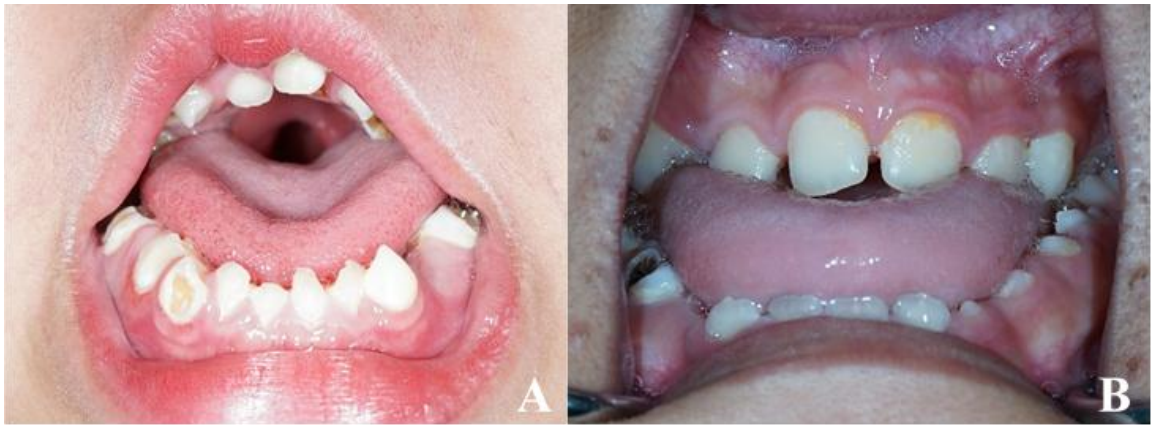

Figure 3 Intraoral images of Patient-1 (A) and Patient-2 (B)
Both patients had Class III malocclusion and anterior open bite

Table 1 Intraoral manifestations of Patient-1 and Patient-2

Manifestations	Patient-1	Patient-2
Cleft palate	Yes	Yes
Anterior open bite	Yes	Yes
Anterior crossbite	Yes	Yes
Posterior crossbite	Yes	Yes
Dental crowding		
- **Maxillary dental arch**	Yes	Yes
- **Mandibular dental arch**	No	No
Congenital missing teeth [a]	No	Yes (13,23)
Supernumerary teeth [a]	No	No
Failure of tooth eruption [a]	Yes	Yes
Oral hygiene status		
- **OHI-S**	2.67	1.33
Caries prevalence		
- **dmft**	13	1
- **DMFT**	0	9
- **dmfs**	29	2
- **DMFS**	0	15
Caries risk assessment	High	High
Maxillomandibular relationship		

	Manifestations	Patient-1	Patient-2
-	**Angle's classification**	Class III malocclusion	Class III malocclusion

[a]*From panoramic radiographs*

Lateral cephalometric analysis

Definition of reference points, reference planes, and angular measurements were specified in Table 2. Lateral cephalometric analysis and measurements in this study were based on the American Board of Orthodontics and Ricketts' analysis (Ricketts, 1957). Thai cephalometric norms were reported in previous studies (Sorathesn, 1988). The cephalometric analysis of Patient-1 and Patient-2 was displayed in Table 3.

Table 2 Definition of lateral cephalometric 2D measurement

Reference points	Definition
1. Glabella (Ga)	The most anterior point of the frontal bone
2. Nasion (N)	The most anterior point of the frontonasal suture
3. Sella (S)	The center of the hypophyseal fossa (pituitary fossa)
4. Porion (Po)	The most superior point of the external auditory canal
5. Orbitale (Or)	The most anteroinferior point of the orbital margin
6. ANS	The tip of the anterior nasal spine
7. PNS	The tip of the posterior nasal spine
8. Point A	The deepest point of the anterior portion of the maxillary alveolar ridge concavity
9. Point B	The deepest point of the anterior portion of the mandibular alveolar ridge concavity
10. Pogonion (Pog)	The most anterior point of mandibular symphysis in the midsagittal plane
11. Gnathion (Gn)	The most anteroinferior point of the bony chin in the midsagittal plane
12. Menton (Me)	The most inferior point of mandibular symphysis in the midsagittal plane
13. Gonion (Go)	The most posteroinferior point on the angle of the mandible
14. Articulare (Ar)	The point of the intersection between the posterior margin of the ascending mandibular ramus and the outer margin of the posterior cranial base
15. Condylar (Co)	The most posterosuperior point on the head of the condyle
16. Basion (Ba)	The most anterior point of the foramen magnum
17. Pterygomaxillary fissure (Ptm)	The most posterosuperior point of the pterygomaxillary fissure
18. Center of cranium point (CC)	The point of intersection between the Ba-N plane and Ptm-Gn plane
Angular and linear measurements	Definition
SN plane	The plane from S to N
Facial plane (NPog)	The plane from N to Pog
FH plane	The horizontal plane through Po and Or
Palatal plane	The plane from ANS to PNS
Occlusal plane	The plane bisecting the occlusion of the first molars and central incisors
Ramus plane	The tangent of the most posterior border of the mandibular ramus through the Ar
Mandibular plane	The lower border of the mandible tangent to the gonial angle and Me
Upper incisor (U1)	The long axis of the maxillary incisor
Lower incisor (L1)	The long axis of the mandibular incisor
E-line	The plane from the soft tissue of the nasal apex to the most prominent point of the soft tissue of the chin
Wits appraisal (AO-BO)	The distance from the perpendicular plane from points A and B to the occlusal plane
U1-NA (mm)	The distance between the tip of the maxillary incisor and a line from Nasion

Reference points	Definition
	to point A
U1-NA	The angle formed by the long axis of the maxillary incisor to the NA plane
U1-L1	the angle formed by the long axis of the maxillary incisor and the long axis of the mandibular incisor
U1-APog (mm)	The distance from the incisal edge of the maxillary incisor to the APog plane
U6-PTV (mm)	The distance from the pterygoid vertical to the distal of the maxillary molar
L1-NB (mm)	the distance between the tip of the mandibular incisor and a line from Nasion to point B
L1-NB	The angle formed by the long axis of the mandibular incisor to the NB plane
L1-APog (mm)	The distance from the incisal edge of the mandibular incisor to APog plane
L1-APog	The angle formed by the long axis of the mandibular incisor to the APog plane
Lower lip to E-line	The distance from the lower lip to E-line
Convexity of point A	The distance from point A to NPog plane
Lower face height	The distance from ANS to Me
Posterior facial height	The distance from S to Gn
Ant cranial base length	The distance from Na to CC
SNA	The angle formed by S, N, A points indicates the sagittal maxillary position
SNB	The angle formed by S, N, B points indicates the sagittal mandibular position
NPog-FH	The angle formed by the FH plane to the NPog plane
ANB	The skeletal relationship between the maxilla and mandible
SN-GoGn	The angle formed by the SN plane and GoGn plane
FMA (FH-MP)	The angle formed by the FH plane and mandibular plane
IMPA (L1-MP)	The angle formed by the long axis of the mandibular incisor to the mandibular plane
Maxillary depth	The angle formed by the FH plane and NA plane
Facial depth	The angle formed by the FH plane and NPog plane
Cranial deflection	The angle between the FH plane and Ba-N plane
Mandibular plane angle	The angle formed by the SN plane and GoMe plane
Mandibular arc	The angle formed by the condylar axis and corpus axis
Facial axis	The angle formed by the NBA plane to the PtmGn plane

Table 3. Lateral cephalometric measurements

Measurements	Thai norm	Range	Patient-1	Patient-2
ABO* format				
- **SNA**	83 ± 4	79 – 87	63	58
- **SNB**	79 ± 3	76 – 82	81	84
- **NPog-FH**	85 ± 2	83 – 87	82	84
- **ANB**	4 ± 2	2 – 6	-18	-26
- **Wits (mm)**	-3 ± 2	(-5) – (-1)	-25	-31.5
- **SN-GoGn**	34 ± 6	28 – 40	51	42.5
- **FMA**	25 ± 4	21 – 29	46	42.5
- **IMPA**	99 ± 4	95 – 103	75.5	75
- **L1-APog (mm)**	5 ± 2	3 – 7	11	14
- **L1-NB**	32 ± 6	26 – 38	25	23
- **L1-NB (mm)**	6 ± 2	4 – 8	4	6
- **U1-NA**	28 ± 4	24 – 32	43	63

- **U1-NA (mm)**	6 ± 2	2 – 8	7	18
- **U1-L1**	118 ± 8	110 – 126	128	130
- **E-line (mm)**	3.5 ± 2	1.5 – 5.5	6.5	7
Ricketts's Analysis				
- **Ant cranial base length**	54.7 ± 2.7 (9 y)	52.0 - 57.4	44	-
(SN-FH)	56.2 ± 2.7 (12	53.5 – 58.9	-	46
- **Maxillary depth**	y)	87.0 – 93.6	67	61
- **Facial depth**	90.3 ± 3.3	81.8 – 88.2	82	-
	85.0 ± 3.2 (9 y)	82.8 – 89.2	-	84
- **Convexity of point A**	86.0 ± 3.2 (12	2.2 – 6.8	-8	-16
- **Cranial deflection**	y)	27.1 – 30.3	26	24
- **Mandibular plane**	4.5 ± 2.3	24.6 – 34.4	45	43
angle	28.7 ± 1.6			
- **Mandibular arc**	29.5 ± 4.9	27.0 – 35.2	42	33
- **Lower face height**		44.7 – 51.1	75	78
- **Facial axis**	31.1 ± 4.1	81.7 – 87.7	77.5	85
- **Posterior facial height**	47.9 ± 3.2	51.7 – 58.3	55	51
- **U6 to PTV (mm)**	84.7 ± 3.0	8.9 - 12.9	-1	-
	55.0 ± 3.3	11.6 – 15.6	-	+4
- **U1 to APog (mm)**	10.9 ± 2 (9 y)	5.3 – 9.7	0.5	3
- **L1 to APog (mm)**	13.6 ± 2 (12 y)	1.9 – 5.7	11.5	-
	7.5 ± 2.2	2.5 – 6.3	-	14
- **L1 to APog**	3.8 ± 1.9 (9 y)	22.5 – 32.1	29	37
- **Lower lip to E-line**	4.4 ± 1.9 (12 y)	1.8 – 5.4	6.5	7.5
(mm)	27.3 ± 4.8			
	3.6 ± 1.8			

** American Board of Orthodontics*

Genetic variants

Genetic analyses by Sanger sequencing revealed that Patient-1 harbored the heterozygous missense variant, c.755C>G (p.Ser252Trp) in the fibroblast growth factor receptor 2 (FGFR2) gene. The variant changes serine to tryptophan at amino acid position 252. Patient-2 possessed the heterozygous missense variant, c.758C>G (p.Pro253Arg) in FGFR2, resulting in the change from proline to arginine at amino acid position 253. The identified pathogenic variants in FGFR2 corresponding with patients' phenotypes indicate that both Patient-1 and Patient-2 are affected by Apert syndrome.

4.2 Discussion

Lateral cephalometric analyses comprising the maxilla position measured by SNA and maxillary depth, and class III maxilla-mandible sagittal relationship measured by ANB and Wits showed that Patient-1 and Patient-2 had retrognathic maxilla. SNB and NPog-FH data indicate that Patient-1 had an orthognathic mandible while Patient-2 has a slightly prognathic mandible. Openbite vertical relationships, upper incisors proclination, lower incisors retroclination, and lower lip protrusion were observed in both patients. These indicate that the patients with Apert syndrome share common facial features including maxillary hypoplasia, anterior open bite, proclined upper incisors, and retroclined lower incisors.

It is known that AS patients have compensatory growth from premature fusion of cranial sutures, which results in an abnormal cranial base relationship (SN-FH). Thus, the sagittal maxillary (SNA) and mandibular position (SNB) can positively deviate from the normal range. Our study suggests that the maxillary and mandibular locations of AS patients in the anteroposterior aspect should analyze from the FH plane which tends to align with the true horizontal plane and more relates to the face than the cranium

(Ellis, and McNamara, 1998). The maxillary depth and facial depth are recommended. According to the results of this study, both patients have retrognathic maxilla with an orthognathic mandible.

The heterozygous variants in the FGFR2 gene have been implicated in Apert syndrome. The variants involve specific two adjacent residues, Ser252Trp and Pro253Arg, predicted to lie in the linker region between IgII and IgIII of the FGFR2 ligand-binding domain. Functional studies showed that Apert-associated variants, compared with wild-type, exhibited a selective decrease in the dissociation kinetics of FGF2. It is indicated that Apert syndrome arises as a result of increased affinity of mutant receptors for specific FGF ligands, leading to FGF signaling activation (Anderson et al., (1998); Das, and Munshi, (2018)). The p.Ser252Trp variant identified in Patient-1 and the p.Pro253Arg in Patient-2 confirmed that both patients were affected with Apert syndrome and the syndrome is caused by the gain-of-function in FGFR2.

Both patients showed generalized gingival inflammation, poor oral hygiene, and high caries risk which are coherent with previous studies (Mufalo et al., (2009); Soanca et al., (2010)). Compared with general Thai children of the same age according to the report of the 8th Thai national oral health survey (2017), both Patient-1 and Patient-2 had higher caries risk. We observed that the patients with Apert syndrome had hypoplastic maxilla, severe teeth crowding, cleft palate, and hand syndactyly. With these physical and oral anomalies, It is difficult for the patients or caregivers to perform proper brushing and oral cleaning. Previous studies have shown that alternative oral care products such as electric toothbrushes, modified toothbrushes for easy gripping, dental floss picks, proxabrushes, high fluoride toothpaste, and non-alcohol fluoride mouthwash should be recommended to the patients with Apert or to their caregivers to improve patients' oral care (Oberoi, Hoffman, and Vargervik, (2012); Tosun, and Sener, (2006)). Additionally, frequent dental check-ups, oral hygiene instruction, oral prophylaxis, and preventive dentistry such as sealant and fluoride application must be implemented(Jose et al., 2021). Multidisciplinary teamwork comprising craniofacial surgeon, neurosurgeon, pediatrician, orthodontist, and pediatric dentists is necessary to deliver proper management of facial deformities and oro-dental abnormalities to improve esthetics and masticatory function of the patients with Apert syndrome (Carpentier et al., 2014).

5. Conclusion

This study reported two patients, one with the p.Ser252Trp variant and another one with the p.Pro253Arg variant in *FGFR2* that causes AS. The patients with AS exhibit craniosynostosis, syndactyly, midface hypoplasia, severe teeth crowing, upper incisor proclination, lower incisor retroclination, and lower lip protrusion. The authors showed that the patients tend to have poor oral hygiene and high caries risk. It is suggested that a multidisciplinary team is essential to deliver prompt management of Cranio-oro-facial abnormalities in the patient with Apert syndrome. Vigilant dental check-ups and oral hygiene care must be implemented for the patients.

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