Cleft Palate in Apert Syndrome

Subjects: Developmental Biology

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Apert syndrome is a rare genetic disorder characterized by craniosynostosis, midface retrusion, and limb anomalies. Cleft palate occurs in a subset of Apert syndrome patients. In Apert syndrome patients, cleft of the soft palate is more frequent than of the hard palate. The length of the hard palate is decreased. Cleft palate is associated most commonly with the S252W variant of FGFR2. In addition to cleft palate, high-arched palate, lateral palatal swelling, or bifid uvula are common in Apert syndrome patients.

Keywords: Apert syndrome ; cleft palate ; FGF ; FGFR2 ; birth defect ; rare disease ; palatogenesis

1. Introduction

Orofacial clefts (OFCs) are the most common craniofacial birth defects [1]. OFCs cause health issues and complications early in life such as feeding problems and ear infections, increasing morbidity and mortality risks [2]. Treatments including surgery, speech therapy, and dental management usually are required. In addition, OFCs cause significant psychological and socioeconomic difficulties for both the patient and the family, and the effects may extend through adulthood [3].

OFCs can be classified as cleft lip with or without cleft palate (CL/P) and cleft palate only (CPO) [1]. The prevalence is 3.1 per 10,000 live births for cleft lip only, 5.6 per 10,000 for cleft lip with cleft palate, and 5.9 per 10,000 for cleft palate only [4]. CPO is a multifactorial disorder caused by both genetic and environmental factors [5][6]. CPO can be categorized into non-syndromic (isolated) and syndromic CPO [5]: non-syndromic CPO is an isolated condition unassociated with any other recognizable anomalies; syndromic CPO is associated with abnormalities in addition to the cleft or with a syndrome with a known genetic etiology [7].

Apert syndrome (MIM #101200) is a congenital disorder characterized by clinical features including multisuture craniosynostosis, midface retrusion, and syndactyly of the hands and feet [8]. It occurs in about 1:80,000 to 1:160,000 live births [9][10][11]. The genetic causes of Apert syndrome are variants affecting the fibroblast growth factor receptor 2 (*FGFR2*) gene. The human *FGFR2* gene is located on chromosome 10q26 and encodes a receptor tyrosine kinase. FGFR2 consists of an extracellular portion composed of three immunoglobulin-like domains (IgI, IgII, and IgIII) responsible for extracellular ligand binding, a transmembrane region, and an intracellular tyrosine kinase domain [12][13][14]. More than 98% of Apert syndrome cases are caused by two amino acid substitutions, Ser252Trp (S252W) and Pro253Arg (P253R), in the linker region between the second and third extracellular Ig domains [15][16]. Approximately 67% of Apert syndrome cases have the S252W variant, while P253R accounts for 32% of cases [15][16][17]. Other rare variants include Ser252Phe (S252F) [17][18][19][20], Ser137Trp (S137W) [21], Alu-element insertions in *FGFR2* [22], and a deletion between *FGFR2* exons IIIb and IIIc creating a chimeric IIIb/IIIc exon [23]. These are all gain-of-function *FGFR2* mutations [24][25].

2. Clinical Characteristics of the Palate in Apert Syndrome

Apert syndrome patients present with anomalies of the palate, which may or may not include cleft palate (**Table 1** and **Table 2**). Cleft palate is present in a subset of affected individuals with Apert syndrome [8] and the frequency is higher than control subjects [26]. However, the incidence of cleft palate in patients with Apert syndrome varies between different studies. Kreiborg and Cohen reported that in a study of 119 patients with Apert syndrome, 75% of the patients had a cleft of the soft palate or bifid uvula [27]. In a group of seven Japanese patients with Apert syndrome, Kobayashi et al. reported two patients with a cleft of the soft palate (28.6%) and one with a cleft of the hard palate (14.3%) [28]. In 17 cases of Apert syndrome reported by Arroyo Carrera et al., cleft palate was identified in 23.5% of patients [29]. In a retrospective study in Brazil, only 1 of 23 (4%) Apert syndrome patients presented with a true cleft palate [30].

Table 1. Palatal phenotypes in cohort studies of Apert syndrome.

Study	Palatal Phenotypes	References
Solomon et al. (1973)	In a cohort of 13 patients, all 13 (100%) presented with a Byzantine palatal arch; 6 of 13 (46%) presented with a bifid uvula; 3 of 13 (23%) presented with a cleft of the soft palate.	[31]
Peterson; Pruzansky (1974)	In a cohort of 19 patients, all 19 (100%) presented with a narrow, high-arched palate with lateral accumulations of soft tissue barely separated by a deep median groove; 6 of 19 (32%) presented with a bifid uvula; 2 of 19 (11%) presented with a cleft palate. On radiographic examination, 10 of 19 (53%) presented with abnormal length of the soft palate, and 8 of 19 (42%) showed abnormal velar thickness (4 overlapping cases).	[32]
Peterson-Falzone et al. (1981)	In a cohort of 29 patients, alterations of the nasopharyngeal architecture were found. Hard palate length was reduced and soft palate length was greater than the norm.	[33]
Kreiborg; Cohen (1992)	In a cohort of 119 patients, almost all patients presented with a Byzantine arch-shaped palate; approximately 75% of patients presented with a cleft of the soft palate or bifid uvula.	[27]
Cohen; Kreiborg (1996)	In a cohort of 136 patients [1], almost all patients (94%) presented with a highly arched, constricted palate and median furrow. Lateral palatal swellings were present that increased in size with age. The hard palate was shorter than normal and the soft palate was both longer and thicker than normal.	[34]
Arroyo Carrera et al. (1999)	In a cohort of 17 patients, 4 of 17 (23.5%) presented with a cleft palate.	[35]
Albuquerque; Cavalcanti (2004)	In a cohort of 5 patients, all (100%) presented with a pseudo-cleft in the midline palate.	[36]
Letra et al. (2007)	In a cohort of 23 patients, 16 of 23 (70%) presented with an arched palate; 21 of 23 (91%) presented with lateral gingival swellings; 1 of 23 (4%) presented with a cleft of the soft palate.	[30]
Stavropoulos et al. (2012)	In a cohort of 23 patients with Apert syndrome and 28 patients with Crouzon syndrome, cleft palate and extensive lateral palatal soft tissue swellings were more common in children with Apert syndrome than Crouzon syndrome.	[37]
Kakutani et al. (2017)	In a cohort of 5 patients, all 5 (100%) had a pseudo-cleft palate with a Byzantine arch shape; 4 of 5 (80%) presented with narrowing in the upper arch.	[38]
Kobayashi et al. (2021)	In a cohort of 7 patients, all 7 (100%) had a high palate with lateral palatal swellings; 2 of 7 (28.6%) presented with a cleft of the soft palate; 1 of 7 (14.3%) presented with a cleft of the hard palate.	[28]
Ogura et al. (2022)	In a cohort of 4 patients, 2 of 4 (50%) presented with a cleft of the soft palate; 1 of 4 (25%) presented with a cleft of the hard palate.	[39]

[1] An enlarged cohort from the study with 119 samples by Kreiborg; Cohen (1992) [27].

Table 2. Palatal phenotypes in case reports of Apert syndrome.

Study	Palatal Phenotypes	References
Batra et al. (2002)	A female patient had a pseudo-cleft palate.	[40]
Vijayalakshmi; Menon (2002)	A male patient had a cleft of the soft palate.	[41]
Huang et al. (2004)	A female patient had a submucous cleft palate and absent uvula.	[42]
Verma et al. (2005)	A male patient had a cleft palate.	[43]
Tosun et al. (2006)	A male patient had a V-shaped maxillary arch with a midline pseudo-cleft and lateral swellings on the palatal process.	[44]
Herman; Siegel (2010)	A female patient with an S252W variant in the *FGFR2* gene had a cleft of the soft palate.	[45]
Premalatha et al. (2010)	A male patient had a high-arched palate with a pseudo-cleft in the posterior one-third.	[46]
Şoancă et al. (2010)	A male patient had a Byzantine arch palate associated with lateral swellings of the palatine processes and a bifid uvula.	[47]
Vadiati Saberi; Shakoorpour (2011)	A female patient had an arched swelling (pseudo-cleft configuration) and a V-shaped maxillary arch.	[48]

Study	Palatal Phenotypes	References
Costa et al. (2012)	A female patient had a U-shaped dental arch, swelling of the lateral palatine processes on both sides, and a bifid uvula.	[49]
Ileri; Goyenc (2012)	A female patient had a cleft palate.	[50]
Khan et al. (2012)	A male patient had a V-shaped maxillary arch and a pseudo-cleft palate.	[51]
Bhatia et al. (2013)	A male patient had a deep pseudo-cleft.	[52]
Aggarwal et al. (2014)	A male patient had a bulky, high-arched V-shaped palate with an occult submucosal cleft and rotated maxillary and mandibular incisors.	[53]
Ercoli et al. (2014)	A male patient had a high-arched palate.	[54]
Kumar et al. (2014)	A male patient had a high-arched palate associated with lateral swellings of the palatine processes on either side of the midline, mimicking a pseudo-cleft.	[55]
Spruijt et al. (2015)	A male patient with an S252W variant in the *FGFR2* gene had a high-arched, narrow palate.	[56]
Barman et al. (2015)	A male patient had a high-arched palate.	[57]
Torres et al. (2015)	A male patient had a high-arched palate. A variant NM_000141.5: c.939+42T>A (T78.501A) located near the splicing site in *FGFR2* was found.	[58]
Işık et al. (2017)	A female patient had a cleft palate.	[59]
Cha et al. (2018)	A male patient had a narrow and triangular-shaped maxillary arch and Byzantine arch-shaped palate.	[60]
Barro et al. (2019)	A female patient had a cleft palate.	[61]
Brajadenta et al. (2019)	An Indonesian male patient with an S252W variant in the *FGFR2* gene had maxillary hypoplasia with a high-arched palate. His V-shaped maxillary arch was filled with double rows of teeth.	[62]
Cammarata-Scalisi et al. (2019)	One of two unrelated female patients, one had a high-arched palate, and the other a cleft of the soft palate. In both patients, a heterozygous S252W variant was identified.	[63]
Dap et al. (2019)	One of two monozygotic twins with an S252W variant was found to have a cleft palate at 30 weeks of gestation.	[64]
Kumar et al. (2019)	A female patient had a high-arched palate, a pseudo-cleft, and gingival enlargement.	[65]
Chavda et al. (2021)	A male patient had a high-arched palate.	[66]
Jose et al. (2021)	A female patient had a pseudo-cleft.	[67]
Tonni et al. (2022)	A female fetus at 20 weeks of gestation was found to have a smooth palate with a midline cleft and an absent uvula. A heterozygous P253R variant was identified.	[73

Cohort studies have shown that a high-arched palate (also described as “high palate”, “pseudo-cleft”, “vaulted palate”, or “Byzantine arch-shaped palate”) with lateral palatal swelling is the most common palatal anomaly in patients with Apert syndrome (**Table 1**), usually present in more than 90% of the patients [28][30][31][32][34][38]. It also is present frequently in case reports of Apert syndrome (**Table 2**). Patients with narrow, high-arched palates and/or gingival swellings [28][30][32][34], may lead to a misdiagnosis of cleft palate in early studies [32].

Apert syndrome has a high frequency of soft palate cleft or bifid uvula [27]. Clefts of the soft palate are more frequent than of the hard palate in patients with Apert syndrome [28][30]. Bifid uvula, which is a split uvula, is often considered as a marker for submucous cleft palate (SMCP) [68][69]. SMCP is a subgroup of cleft palate resulting from insufficient medial fusion of the muscles of the soft palate during palatogenesis [69]. A submucous cleft palate may appear to be structurally intact, but other defects may be present, including a bony notch in the hard palate, a bluish line at the midline of the soft palate (zona pellucida), and a bifid uvula [70][71].

In addition to the clefts, decreased length of the hard palate has been observed in patients with Apert syndrome [33][72]. This may indicate defects in palatal bone formation caused by the pathogenic FGFR2 variant, or it could be secondary to midface hypoplasia, which is one of the features of Apert syndrome.

Genotype–phenotype correlations in Apert syndrome have been studied. Although these correlations are variable, cleft palate is associated more commonly with the S252W variant than P253R in multiple studies comparing subgroups defined

by these two variants in FGFR2 [16][17][73][74][75][76]. Cleft palate is present in approximately 60% of patients with the S252W variant and 15% of patients with the P253R variant (**Table 3**), suggesting this genotype–phenotype correlation in Apert syndrome.

Table 3. Genotype–phenotype correlations of cleft palate with the FGFR2 S252W and P253R variants.

Study	Cohort			FGFR2 S252W		FGFR2 P253R		Notes	References
	Cohort Size	Abnormal Palate Number	%	Cleft Palate Fraction	Cleft Palate %	Cleft Palate Fraction	Cleft Palate %		
Park et al. (1995)	36	Cleft palate in 16 patients	44.4	15/16	93.8	1/16	6.2		[16]
Slaney et al. (1996)	87	Soft palate cleft or bifid uvula in 37 patients	42.5	24/41	58.5	4/23	17.4		[73]
Lajeunie et al. (1999)	36	Cleft palate in 15 patients	41.7	12/23	52.2	2/12	16.7	One fetus with the S252F mutation also had a cleft palate	[17]
Sakai et al. (2001)	6	Cleft palate in 5 patients	83.3	5/5	100.0	0/1	0.0		[76]
Von Gernet et al. (2000)	21	Cleft palate in 11 patients	52.4	9/15	60.0	2/6	33.3		[74]
Kilcoyne et al. (2022)	51	Cleft palate or bifid uvula in 26 patients.	51.0	18/28	64.3	8/23	34.8		[75]

3. Open Questions and Future Directions

In patients with Apert syndrome, high-arched palate with lateral palatal swelling is the most common palatal anomaly (70–100%, **Table 1**). Approximately 50% of patients presented with cleft palate (**Table 1** and **Table 3**), and 30% of patients presented with bifid uvula [32][77]. The incidence of cleft palate and other palatal defects in patients with Apert syndrome varies between different studies. This may be caused by factors such as genetic background, environmental effects, variability of phenotypes, and diagnostic criteria across studies.

Craniosynostosis is a diagnostic feature of Apert syndrome. Almost all Apert patients have coronal craniosynostosis, and a majority have sagittal and lambdoid craniosynostosis [8][34]. A subset of affected individuals have cleft palate. A wide array of other abnormalities is seen in Apert syndrome patients, including craniofacial malformations, syndactyly, feeding problems, cognitive disorders, hearing loss, and speech and language difficulties. Thus, a multidisciplinary team is essential to provide treatment and care. For cleft palate, various treatments including surgery, dental management, speech therapy, and psychological support are required [2]. Palate repair surgery is typically performed prior to development of pressure consonants to improve speech production and intelligibility [8]. However, patients may experience lifelong psychosocial effects from the malformation of the facial appearance even after surgeries [2]. Future studies can be performed to determine if there is a correlation between the palatal phenotype and other phenotypes and management issues in Apert syndrome.

Various potential therapies are emerging to remedy cleft palate. One potential therapeutic avenue applicable to Apert syndrome is targeting of FGFR activity and downstream signaling pathways. For example, coronal suture fusion in calvarial explants was decreased by exposure to the MEK1 inhibitor PD98059 in the FGFR2 P253R model [78]. Both pre- and postnatal administrations of the MEK1/2 inhibitor U0126 alleviated symptoms in the FGFR2 S252W model, as did a gene therapy strategy of expressing a short hairpin RNA against the *Fgfr2*^{S252W} allele [79]. FGFR2-related signaling network analysis may help to find targets for novel drugs to treat or alleviate symptoms. In addition, innovative cellular therapeutics such as stem cell transplantation have been applied in cleft palate treatment [80][81]. Mazzetti et al. reported results from patients with cleft lip and palate who had stem cells from umbilical cord blood and placental blood injected into the bone and soft tissue during the primary surgical repair procedure. Compared to controls, the group with stem cell

injection showed improvement in the inflammatory response, fewer postoperative complications and less fibrosis. Tomography showed an improved maxillary alignment, and the alveolar cleft became smaller [81].

High-arched palate has been reported in ciliopathy-related syndromes [82][83]. Ciliopathies are disorders that arise from the dysfunction of motile and/or non-motile cilia [84], with craniofacial dysmorphology as a common feature [83]. An etiological link between ciliopathies and FGF hyperactivation syndromes has been identified [83]. The primary cilium is the central organelle for the transduction of the hedgehog signaling pathway in vertebrates and is also a signaling center for other signaling pathways, such as WNT, Notch, Hippo, GPCR, PDGF, and other RTKs including FGF, mTOR, and TGF-β [85][86]. Considering that FGF signaling regulates the formation of primary cilia [86], it would be interesting to investigate the roles of cilia and associated signaling pathways in the palatal defects in Apert syndrome, especially the high-arched palate.

4. Conclusion

Apert syndrome is a rare genetic disorder caused by pathogenic variants of the *FGFR2* gene. Cleft palate is a common phenotype in Apert syndrome cases, and high arched palate, lateral palatal swelling, and bifid uvula also occur with high frequency. Palatal defects in Apert syndrome inform the critical role of FGFR2 in the regulatory network for palatogenesis. Mouse models of Apert syndrome have been established and display many phenotypes of Apert syndrome. In mouse models of FGFR2 S252W and FGFR2 P253R, incomplete closure of the anterior end of the secondary palate occurs in newborn mice. These models provide opportunities for in vivo investigation of the role of FGF signaling in palatal defects in Apert syndrome.

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