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Dental agenesis in Kallmann syndrome individuals with *FGFR1* mutations

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Background. Kallmann syndrome (KS) is a rare genetic disorder characterised by central hypogonadism with a lack of sense of smell and in some cases renal aplasia, deafness, syndactyly, cleft lip/palate, and dental agenesis. To date, five genes for KS have been identified: *KAL1*, located on the X chromosome, and *FGFR1*, *PROKR2*, *PROK2* and *FGF8*, which are involved in autosomally transmitted forms of KS.

Aim. The study characterised the dental ageneses of individuals with KS associated with mutations in the *FGFR1* gene.

Design. Six individuals displaying dental agenesis were included. Clinical and radiological dental evaluations as well as medical anamneses were carried out.

Results. Microdontia, screwdriver-shaped mandibular incisors, thin molar roots, and patterns of dental agenesis in both dentitions were observed. One to nine teeth were missing, most frequently, in descending order, lateral mandibular incisors, second premolars of upper and lower jaws, and lateral maxillary incisors. The pattern of dental agenesis is associated with four new mutations in the *FGFR1* gene. Conclusion: Dental agenesis may be a clinical feature of Kallmann syndrome caused by a mutation in the *FGFR1* gene. These findings highlight the role that odontologists can play in the early diagnosis and treatment of gonadotropic deficiency.

Introduction

Kallmann syndrome (KS, OMIM 147950) is a rare genetic disorder characterised by central hypogonadism, the absence of spontaneous puberty due to a deficiency of gonadotropin-releasing hormone (GnRH), which is secreted by the hypothalamus, and a complete (anosmia) or partial (hyposmia) lack of a sense of smell. Developmental deficiency, including facial and oral developmental defects such as cleft lip/palate (CLP) and dental agenesis, has also been described.[1] The prevalence of KS is estimated at 1/8000 in males and 1/40,000 in females, but is probably underestimated.[2] To date, five genes that cause KS have been identified: *KAL1* (Kallmann syndrome sequence 1/anosmin-1, KAL1, Xp22.3, OMIM 308700) located on the X chromosome, *FGFR1* (fibroblast growth factor receptor 1, KAL2, 8p12, OMIM 136350), *PROKR2* (Prokineticin Receptor 2, KAL3, 20p13, OMIM 607123), *PROK2* (Prokineticin 2, KAL4, 3p21.1, OMIM 607002), and *FGF8* (fibroblast growth factor 8, KAL6, 10q24, OMIM 612702) which are involved in the autosomally transmitted forms of KS.[3] Most individuals with *KAL1* mutations have hypogonadism and variable degree of anosmia. In contrast, the phenotype of KS due to *FGFR1* mutations is highly variable with several degrees of hypogonadism and hyposmia, and in few patients normal sense of smell has been reported.[4] Several malformations as renal unilateral agenesis, deafness, and syndactyly have been described in *KAL1* and *FGFR1* mutated KS subjects.[5] Individuals with mutations in the *PROKR2* or *PROK2* genes display variable degrees of olfactory and endocrine

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dysfunctions and associated malformations appear less frequent.[6] Approximately 10% of Caucasian[7] and Japanese[1] individuals with KS have loss-of-function mutations in *FGFR1*. To treat KS, hormonal replacement therapy induces puberty, and later, fertility. There is no current treatment for anosmia. With treatment, onset of puberty occurs in all cases, and fertility is achieved in most cases. Constitutive *FGFR1* mutations also cause two skeletal diseases, Pfeiffer syndrome type 1 (OMIM 101600) and osteoglophonic dysplasia (OMIM 166250).

The prevalence of the congenital absence of one or more teeth in the normal population ranges from 3.2 to 7.6%, depending on gender and ethnic origin.[8] The agenesis of lateral maxillary incisors and second premolars with no other associated malformations is a common phenotype.[9] There are many different patterns of tooth agenesis, some of them are isolated and others are syndromic.[10]

Thirty percent of individuals with KS have CLP while 5–10% exhibit tooth agenesis.[7] The expression of FGFR1 in the condensed mesenchyme, then in the enamel epithelium and papillary mesenchyme during the morphogenesis of human tooth germs may explain, in part, how mutations that inactivate this receptor can cause tooth agenesis.[11] However, very few publications specify the teeth involved and the oral phenotype (Table 1). The aim of the present study was to characterise the ageneses of individuals with KS and their correlations with *FGFR1* mutations.

Materials and methods

Six individuals, four males and two females, were included in the study, all bear a *FGFR1* mutation. They were chosen among a large population of 40 KS patients, in whom molecular investigation revealed mutations in one of the five KS genes. The average age of the individuals was 25 years and ranged from 3 to 57. Clinical data of the individuals were obtained from the referring endocrinologists. They all had an orthopantomogram and one had a clinical oral examination. The ethics committee of the Paris 7 Dental University approved this study.

Clinical data, oro-facial phenotype, and the molecular diagnosis of KS were recorded. The orthopantomograms were analysed to assess dental agenesis, root morphology, and possible dental anomalies. All teeth were examined, with the exception of third molars. Extraction due to decay, orthodontic treatment or periodontal disease, and loss of teeth due to dental trauma were recorded by questioning parents and/or patients.

Results

A summary of the clinical data (endocrine and olfactory), the identified mutations of *FGFR1* and the oral phenotypes are provided in Table 2. Three patients reported normal sense of smell. Among the three mutations found in the tyrosine kinase domain, two mutations were previously documented[4,5] and one substitution was identified (c.2069T>G p.Leu690-Pro). Three novel mutations were found in the third immunoglobulin-like domain: two amino-acid substitutions (c.1023C>G p.Cys-341Trp; c.1042G>A p.Gly348Arg), and one deletion (c.841del6) leading to deletion of Ser281 and Asp282 residues.

Number of teeth

The number of missing teeth, ranged from one to nine in the six subjects, was evaluated by orthopantomogram. An overall number of 23 missing teeth was observed. A 3-year-old subject exhibited agenesis of six primary incisors (subject 2 in Table 2). This young patient did not have his permanent dentition assessed. The most frequently missing permanent teeth were lateral mandibular incisors (5/23), second premolars (maxillary: 4/23, mandibular: 4/23), and lateral maxillary incisors (3/23). Agenesis of central incisors (maxillary: 2/23, mandibular: 2/23), second mandibular molars (2/23), and a first mandibular molar (1/23) were also observed.

Tooth size and shape

Patient 1 had small and screwdriver-shaped mandibular incisors as well as microdontia of the first maxillary premolars, with

Table 1. Literature review of the orodental phenotype in Kallmann syndrome.

	Number of subjects	Puberty (number of subjects)	Anosmia (number of subjects)	Orodental phenotype	CLP/CP	Molecular diagnosis
Hardelin *et al.* 1993 [31]	2	2 Delayed puberty	2	One subject with agenesis: one premolar	No	X-linked KS
Abs *et al.* 1994 [32]	1	2 Delayed puberty	0	Agenesis: 17,15,14 (or 24), 12, 22, 25, 27, 47, 45, 35, 37	No	No
De Zegher *et al.* 1995 [16]	6 independent subjects	5 Delayed puberty	1	Agenesis: 12, 22	No	No
Molsted *et al.* 1997 [17]	11	11 No puberty	11	No agenesis: 5 subjects Agenesis: 15 or 25: 2 subjects Agenesis: 15, 25, 35, 45: 2 subjects Agenesis: 15, 14, 12, 22, 24, 25, 35 Agenesis: 14, 12, 22	No No No No CLP CLP	No
Dodé *et al.* 2003 [7]	Mother and 2 siblings	2 Spontaneous puberty, 1 NR	1	All three: 7 to 8 teeth missing	No	*FGFR1*
Sato *et al.* 2004 [1]	1	1 Delayed puberty	NR	4 permanent teeth	No	No *KAL1* or *FGFR1* mutation
Albuisson *et al.* 2005 [13]	1	NR	1	Dental agenesis	CP	*FGFR1*
Pitteloud *et al.* 2006 [4]	1	NR	No	2 congenitally missing teeth	No	*FGFR1* mutation in TKD
	1	NR	1	3 missing teeth	CLP	*FGFR1* mutation in TKD
Zenaty *et al.* 2006 [5]	1	/	/	Median central incisor	No	*FGFR1* mutation (de novo)
	1*	/	1	Multiple dental agenesis (mother with dental agenesis)	No	*FGFR1* mutation (de novo)
Sato *et al.* 2006 [14]	2: Son	No puberty	1	Dental agenesis 16, 15, 14, 24, 25, 26, 46, 43, 33, 36	No	*FGFR1*
	Mother	Normal	1	Dental agenesis 16, 26 46, 43, 33, 36	No	*FGFR1* Somatic mutation
Riley *et al.* 2007 [15]	1	Normal	1	Dental agenesis 13, 24	CLP	*FGFR1*
Dodé *et al.* 2007 [26]	1	Hypogonadism	1	Dental agenesis	No	*FGFR1*

CP: cleft palate, CLP: cleft lip palate, KS: Kallmann syndrome, *FGFR1*: fibroblast growth factor receptor 1 gene, KAL1 Kallmann syndrome sequence 1 (anosmin-1), NR: no reported, /: subject too young to evaluate puberty.
Missing teeth are numbered based on the World Dental Federation ISO-3950 notation, TKD: tyrosine kinase domain.
*The clinical features of this subject are described in Table 2 (subject 1).

hypo-development of the lingual cusps and flat vestibular cusp, which resulted in a cubic crown morphology (Figs 1 and 2). The other orthopantomograms showed long, thin roots, this being seen mainly in the first molars (Fig. 3).

Tooth position

A rotation of premolars in subject 1 was the only observed anomaly.

Discussion

We report the analysis of the orthopantomograms of six subjects and the oral examination of one subject with KS caused by loss-of-function mutations in *FGFR1*. For this rare condition, individuals were followed up in the departments of Endocrinology at different hospitals in the country and regrettably, only one had an extensive oral examination. Dental agenesis was established

Table 2. Clinical data and oral phenotypes of the six subjects with a *FGFR1* mutation.

Subject	Age	Gender	Mutation	Anosmia	HH	Clinical features	Clefts	Dental agenesis	Supplementary dental features
1	17	Male	c.1864 C>G Arg622Gly	+ (agenesis of olfactory bulbs)	+	Bilateral cryptorchidism without micropenis, Multiple fusions of metacarpal bones on hands and feet, Right ear hypoplasia		15,12, 22, 25, 45, 42, 32, 35	Remaining temporary teeth: 55, 65, 75, and 85 Microdontia Abnormal crown morphology Familial anamnesis of dental agenesis
2	3	Male	c.1865 G>A Arg622Gln	No	+	Unilateral cryptorchidism with severe micropenis	CLP unilateral	52, 51, 61, 62, 72, 82	
3	57	Male	c.1023C>G Cys341Trp	+	+	Low testicular volume Osteopenia of lumbar vertebrae and femoral neck hyperkalemia		15, 36, 47	
4	21	Male	c.2069T>G Leu690Pro	+	+	Micropenis and microtestes Osteoporosis of vertebrae		41, 31	Apical infection: 36 Remaining temporary teeth: 71, 81, 82 Long, thin roots
5	32	Female	c.841del6 281delSD	+	+	Primary amenorrhea		32	Cementoma: 36 Long, thin roots
6	18	Female	c.1042 G>A Gly348Arg	No	+	Pituitary hypoplasia, partial GH deficiency	CLP	15,12,11,21, 47 45, 42, 32, 35,	Remaining temporary teeth: 73 Long, weak roots

HH: hypogonadotropic hypogonadism, CLP: cleft lip palate, *FGFR1*: fibroblast growth factor receptor 1 gene, GH: growth hormone, Missing teeth are numbered based on the World Dental Federation ISO-3950 notation.

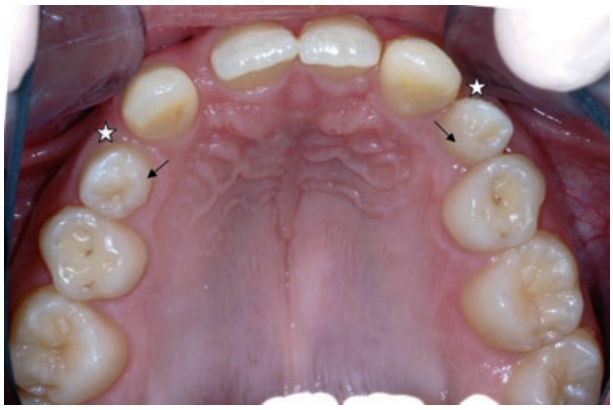

Fig. 1. Occlusal view of the maxillary teeth of subject 1 at 17 years of age, showing microdontia (star) of the first maxillary premolars with hypo-development of the lingual cusps (arrow).

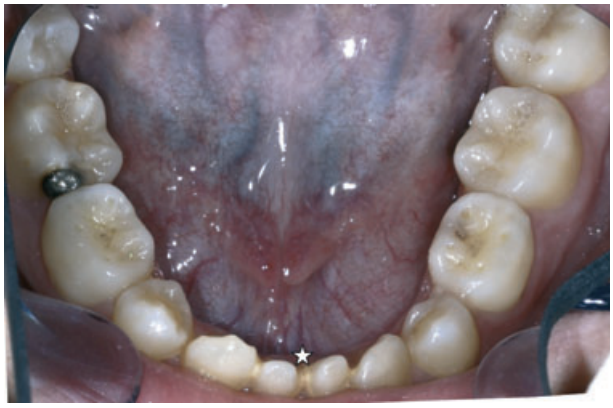

Fig. 2. Occlusal view of the mandibular teeth of subject 1 at 17 years of age, showing microdontia (star) of the permanent central incisors.

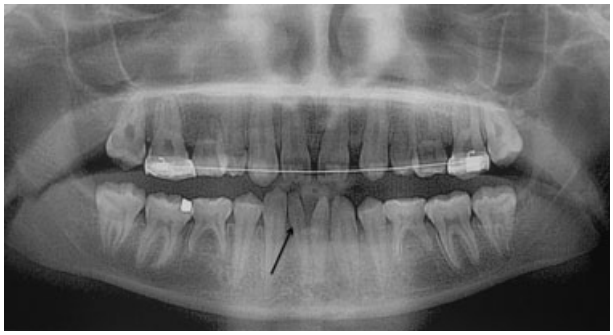

Fig. 3. Orthopantomogram of subject 1 at 17 years of age, showing dental agenesis of teeth: 12, 22, 15, 25, 32, 42, 35, 45; persistent second primary molars: 55, 65, 75, 85; microdontia of the first maxillary premolars and screwdriver-shaped mandibular incisors with deviating crowns (arrow).

after questioning for possible extractions or dental trauma, which could lead to an overestimation of the number of agenesis. Furthermore, the ageneses of permanent teeth suspected in the subject of a three-year-old were not taken into account. Among the six individuals included in this study, two had unilateral cleft lip/palate (CLP). Congenitally missing teeth are more frequent in population with CLP.[12] The prevalence of CLP (2/6) in the present study was similar to other studies: 5/19,[7] 1/3,[4] 2/7.[13] It confirms that severe oligodontia may be present in subjects without any CLP and therefore emphasizes the importance of an extensive oro-dental examination for every patient with congenital gonadotropic deficiency.

The present study highlights the phenotype of dental agenesis in KS. The most frequently missing permanent teeth are, in descending order, lateral mandibular incisors, second premolars, and lateral maxillary incisors. In previous studies in which molecular diagnosis was carried out, the pattern differs. The missing teeth, in descending order, are first molars (8/18), canines (5/18), and first premolars (5/18).[14,15] Other studies, which did not involve molecular diagnoses, reported that second premolars and lateral incisors are often missing.[16,17] So, the patterns of tooth agenesis in KS show a great variability, and no specific pattern could be detected.

Various genetic syndromes lead to specific patterns of tooth agenesis.[10] *MSX1* and *EDA* mutations are respectively involved in Witkop syndrome[18] and hypohidrotic ectodermal dysplasia[19] in which dental agenesis contributes to the phenotype. *MSX1* mutations have also been linked to hypo/oligodontia with or without cleft lip palate,[20,21] while an *EDA* mutation has been associated with dental agenesis without CLP.[22] *MSX1* mutations are also associated with maxillary premolar and second mandibular premolar agenesis, *EDA* mutations with incisor and canine agenesis, and *PAX9* mutations with second molar and first molar agenesis.[23] Conversely to *EDA*, *PAX9* and *MSX1* mutations, mutations in *FGFR1* do not appear linked to specific tooth agenesis.

Vieira *et al.* recently showed that isolated maxillary premolar agenesis in absence of any gonadotropic deficiency may be associated with an allele marker of *FGFR1*.[21] The phenotype of the mother of subject 1, was restricted to dental agenesis.[5] Similarly to *MSX1*, these data indicate that *FGFR1* is indeed a candidate gene for isolated dental agenesis.

The same mutation in *FGFR1* can lead to different missing teeth.[5,14] No clear phenotype–genotype relationship between phenotypes of dental agenesis and *FGFR1* mutations could be established in this and previous studies.[14,15] Moreover, the endocrine and olfactory data of the subjects display great variability. These variations in genotype/phenotype for dental agenesis, which confirm the variable expressivity of *FGFR1* mutations, may be related to environmental or epigenetic factors or modifier genes.[21,24]

The *FGFR1* gene encodes a membrane receptor with three extracellular immunoglobulin-like domains (Igl) and an intracellular tyrosine kinase domain (TKD).[25] Ligand binding results in receptor dimerization and the recruitment of intracellular signalling proteins. In this study, four novel mutations in the *FGFR1* gene are documented. Three are caused by substitutions in the tyrosine kinase domain or immunoglobulin-like domain III (Igl-III). One is a deletion of two residues in the Igl-III-domain without frameshift involvement. To our knowledge, two different mutations located in tyrosine kinase domain of the *FGFR1* gene are linked with the phenotype of dental ageneses.[14,15] To date, eight mutations of the *FGFR1* gene were associated with congenitally missing teeth.[4,5,7,13–15,26]

According to Molsted *et al.*,[17] microdontia and abnormal crown morphology of premolars and incisors was observed. Screwdriver-shaped incisors are also a well-known clinical feature of Nance-Horan and Williams syndromes.[27,28] However, there are very few reports in the literature on the hypo-development of the lingual cusp of premolars.[29] We also observed that the roots tended to be long and thin, and one individual was affected by a cementoma. In contrast, we found no taurodontism or root resorption. Tissue-specific inactivation of the two alleles of *Fgfr1* in mice results in severe enamel defects that mimic amelogenesis imperfecta.[30] The individual in our study who had a dental examination (subject 1) have no enamel defect.

To our knowledge, only one individual with KS due to a mutation in *KAL1* has been described with agenesis of a premolar,[31] which is the most frequently missing congenital tooth in Caucasian populations.[8] A molar agenesis has been reported in one individual with KS due to *PROK2* mutations.[6] However, additional studies are required to confirm the higher prevalence of dental agenesis in KS subjects with *FGFR1* mutations.

The diagnosis of the KS is usually established at puberty in females, while gonadotropic deficiency is frequently diagnosed at birth in males with a micropenis or bilateral cryptorchidism. In the case of dental agenesis, odontologists have to look for a partial or a complete lack of smell, delayed puberty in females or clinical signs of hypogonadism in males to suggest the diagnosis of Kallmann syndrome. The present study indicates that dental agenesis may be a valuable clinical sign suggestive of *FGFR1* mutations. This approach may lead to earlier diagnosis and treatment of gonadotropic deficiency.

What this paper adds

- This paper provides information on clinical medical data and the patterns of teeth agenesis in the six subjects with Kallmann syndrome due to mutations in *FGFR1*.
- The present study identifies four new mutations in *FGFR1* linked with tooth agenesis.
- This paper gives information to dentists such as orthodontists, prosthodontists, oral surgeons and, of course, general dentists.

Why this paper is important to paediatric dentists

- In the case of dental agenesis, paediatric dentists need to look for a partial or complete lack of smell, and delayed puberty, which would suggest the diagnosis of Kallmann syndrome.
- It contains information for paediatric dentists who can contribute to an earlier diagnosis and endocrine treatment.

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