Clinical Review

Journal of Dental Research
2018, Vol. 97(12) 1306–1316

DOI: 10.1177/0022034518777460
journals.sagepub.com/home/jdr

Patterns of Dental Agenesis Highlight the Nature of the Causative Mutated Genes

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Abstract

The most common outcome of defective dental morphogenesis in human patients is dental agenesis (absence of teeth). This may affect either the primary or permanent dentition and can range from 5 or fewer missing teeth (hypodontia), 6 or more (oligodontia), to complete absence of teeth (anodontia). Both isolated and syndromic dental agenesis have been reported to be associated with a large number of mutated genes. The aim of this review was to analyze the dental phenotypes of syndromic and nonsyndromic dental agenesis linked to gene mutations. A systematic review of the literature focusing on genes (*MSX1, PAX9, AXIN2, PITX2, WNT10A, NEMO, EDA, EDAR, EDARADD, GREMLIN2, LTBP3, LRP6*, and *SMOC2*) known to be involved in dental agenesis was performed and included 101 articles. A meta-analysis was performed using the dental phenotypes of 522 patients. The total number and type of missing teeth were analyzed for each mutated gene. The percentages of missing teeth for each gene were compared to determine correlations between genotypes and phenotypes. Third molar agenesis was included in the clinical phenotype assessment. The findings show that isolated dental agenesis exists as part of a spectrum of syndromes for all the identified genes except *PAX9* and that the pattern of dental agenesis can be useful in clinical diagnosis to identify (or narrow) the causative gene mutations. While third molar agenesis was the most frequent type of dental agenesis, affecting 70% of patients, it was described in only 30% of patients with *EDA* gene mutations. This study shows that the pattern of dental agenesis gives information about the mutated gene and could guide molecular diagnosis for geneticists.

Keywords: systematic review, evidence-based dentistry, PAX9, EDA, MSX1, WNT10A

Introduction

Dental agenesis, or absence of teeth, affects 5.5% of Europeans (Polder et al. 2004). Up to 80% of patients with dental agenesis are missing only 1 or 2 teeth. Trauma, chemotherapy, and vascular anomalies are rare causes of missing teeth in childhood. However, the main causes of dental agenesis are genetic mutations, although DNA polymorphisms and methylations have also recently been highlighted for their role in this pathology (Hlousková et al. 2015; Wang et al. 2016). Dental agenesis may occur in isolation or as part of a syndrome. Nonsyndromic dental agenesis is classically associated with mutations in 4 genes: *PAX9, MSX1, WNT10A*, and *AXIN2* (De Coster et al. 2009; van den Boogaard et al. 2012). However, recent reports of cases of isolated dental agenesis have implicated additional genetic mutations, usually in association with syndromes (for descriptions, see the Appendix Table). For example, *EDA* encodes ectodysplasin-A and is involved in anhidrotic ectodermal dysplasia (EDA) and hypohidrotic ectodermal dysplasia (HED), which present as hypohidrosis or anhidrosis, hypotrichosis or alopecia, and oligodontia or anodontia (Arte et al. 2013). Ectodermal dysplasia is associated with a large group of syndromes characterized by anomalies in at least 2 ectodermally derived structures (e.g., hair, nails, sweat glands, and teeth). However, some case studies have reported *EDA* mutations with no associated ectodermal phenotype other than dental agenesis.

Oligodontia, the agenesis of 6 or more teeth, is less common than hypodontia, the agenesis of 1 to 5 teeth. Anodontia, the agenesis of all the dentition, is observed in even fewer cases. A previous meta-analysis of 17 studies showed an

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A supplemental appendix to this article is available online.

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oligodontia prevalence of 0.14% (Polder et al. 2004). In that study, the most commonly missing teeth were mandibular second premolars (2.91%–3.22%), followed by maxillary lateral incisors (1.55%–1.78%) and mandibular second premolars (1.39%–1.61%). The prevalence of third molar agenesis ranged from 9% to 20% (Lavelle et al. 1970; Levesque et al. 1981). Although the third molars are the most commonly missing teeth, they are usually excluded from phenotypic descriptions of patients with dental agenesis. However, some patient descriptions of oligodontia do report third molar presence, and so we included an assessment of third molar agenesis in our review.

Patients with hypodontia are often described with lateral incisor and second premolar agenesis, which are the most commonly missing teeth. Patients who experience agenesis of a less commonly involved tooth (e.g., canine or maxillary central incisor) more often present with many missing teeth. Indeed, first molars and maxillary central incisors were the least affected teeth, absent in only 0% to 0.05% of cases (Polder et al. 2004).

Previous agenesis research has focused on either phenotype or genotype but not the relationship between them. Through this systematic review and analysis, we aimed to characterize and correlate dental agenesis phenotypes with their causative genetic mutations.

Materials and Methods

Bibliographic Search

A systematic MEDLINE search covering 1986 through June 2016 was performed to identify articles concerning genotypes and phenotypes of dental agenesis. The MEDLINE search used the following Medical Subject Heading (MESH) terms (or the gene name when the MESH term did not exist) with the "humans" filter: "MSX1," "PAX9," "AXIN2," "PITX2," "WNT10A," "NEMO," "EDA," "EDAR," "EDARADD," "GREMLIN2," "LTBP3," "LRP6," "SMOC2," and "mutations." These genes were chosen because they were mentioned in recent publications about dental molecular genetics (Chhabra et al. 2014; Prasad et al. 2016). References from selected articles were also checked. Finally, English-language articles were retained if they contained information on the following 2 topics: 1) a genetic mutation from the above list and 2) a description of a dental phenotype (e.g., radiograph, odontogram). Digenic mutations (e.g., mutations in both *EDAR* and *WNT10A*) and articles about gene polymorphisms were excluded. Finally, redundant articles were excluded.

Data Extraction and Analysis

Three independent reviewers (B.P.F., M.H.B., and M.L.D.M.) extracted the data. Gene mutation, phenotype diagnosis, and mode of inheritance were recorded. All available clinical images were carefully analyzed to improve the description of dental agenesis in permanent teeth. When available, data for each affected relative were also collected. Genetic mutations were checked for each patient. The type and number of missing teeth were recorded for each patient.

The mean number of missing teeth, the number of patients affected by hypodontia and oligodontia, and the total number of patients with each gene mutation and each missing tooth were calculated. To determine correlations between phenotype and genotype, percentages of missing teeth were calculated for the maxillary and mandibular arches (pooling the right and left sides) and expressed with respect to the total number of teeth analyzed and the total number of patients affected. The occurrence of dental agenesis was divided into 3 groups: "common," more than 50% absence; "less common," 30% to 50% absence; and "rare," less than 30% absence. Nonparametric tests and the Kruskal-Wallis test with Dunn's modification were performed to compare data. P values were calculated as follows: $*P < .05$, $**P < .01$, and $***P < .001$.

Results

In total, 101 articles describing 522 patients were included in the analysis (Fig. 1). No analysis could be performed for the *LTPB3, SMOC2*, and *LRP6* genes because data on missing teeth were not available. For *PITX2, NEMO*, and *GREMLIN2*, see Appendix Figure 1.

Missing Teeth

Taken together, the data present in these 101 articles allow us to define 3 dental agenesis groups based on the frequency of tooth absence (common, less common, and rare—see Materials and Methods for details). In the common agenesis group, the following teeth were missing: $_{max}$Mo3 (72.60%), $_{mand}$Mo3 (70.91%), $_{max}$PM2 (61.57%), $_{mand}$PM2 (55.52%), and $_{max}$LI (50.77%). Less common agenesis was noted for $_{mand}$CI (49.90%), $_{mand}$Mo2 (42.39%), $_{max}$PM1 (41.87%), $_{max}$Mo2 (40.73%), and $_{mand}$ LI (34.52%). Rare agenesis was observed for $_{max}$Mo1 (29.64%), $_{max}$Ca (27.05%), $_{mand}$PM1 (24.75%), $_{mand}$Mo1 (22.58%), $_{mand}$Ca (17.23%), and $_{max}$CI (10.61%) (Fig. 2A). The average number of missing teeth varied depending on the genetic mutation considered. For example, the average number of missing teeth was 11.54 for mutation of *MSX1*, 12.84 for *PAX9*, 11.11 for *EDA*, 10.26 for *EDAR*, 11.14 for *EDARADD*, 13.11 for *WNT10A*, 12.45 for *PITX2*, 3.50 for *NEMO*, and 5.40 for *GREMLIN2* (Fig. 2B). Third molars were clearly the most frequent missing teeth, but our analysis revealed some differences depending on the mutated gene. Patients with mutations in either the *EDA* or *EDAR* gene showed less third molar agenesis compared to patients with mutations in other genes (Fig. 2C). However, this was not true for patients affected by HED. In the following sections, we describe the specific agenesis profiles for each of the genes implicated in dental agenesis.

MSX1 *Dental Phenotype*

The 21 articles reporting *MSX1* mutations included 80 patients with 24 different mutations (Appendix Table). Patients with *MSX1* mutations showed isolated dental agenesis (62.02%) (MIM#106600), oral clefts (21.25%) (MIM#608874), Witkop syndrome (10%) (MIM#189500), or Wolf-Hirschhorn

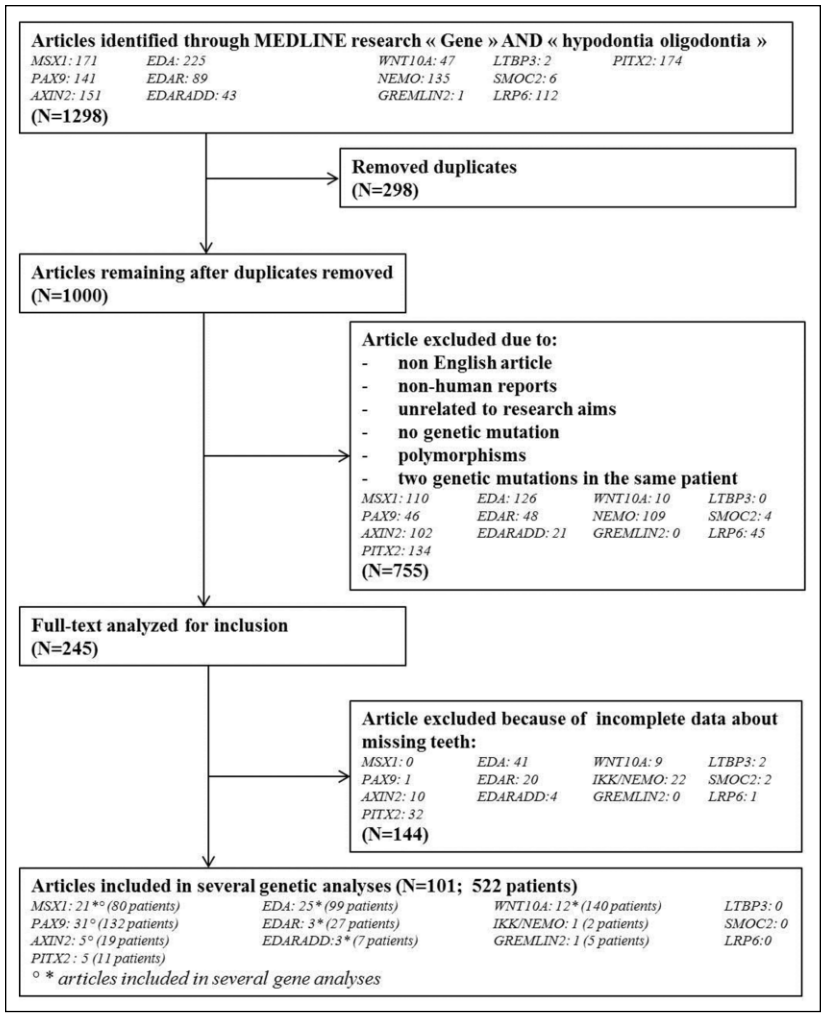

Figure 1. Flowchart of the literature search and article selection processes. In total, 101 articles were included.

syndrome (6.25%) (MIM#194190) (Table 1). *MSX1* mutations were also linked to nonsyndromic lip and palate clefts (Butali et al. 2011). A single mutation (c.453 G>T) was described in 2 unrelated families, one with isolated dental agenesis (Kamamoto et al. 2011) and the other with tooth agenesis and unilateral lip and palate cleft (van den Boogaard et al. 2000; Jezewski et al. 2003).

The number of missing teeth ranged from 1 to 28 (mean, 11.54). Hypodontia was present in 11.25% of patients and oligodontia in 88.75%. Exclusive hypodontia with agenesis of the second premolar and maxillary lateral incisor was associated with the p.Arg151Ser mutation. A high percentage of agenesis was noted for $_{max}$PM2 (86.71%), $_{mand}$PM2 (83.75%), $_{max}$Mo3 (83.85%), $_{mand}$Mo3 (86.03%), and $_{max}$PM1 (57.59%). In contrast, only 30.38% of maxillary lateral incisors were missing (36.71% of patients) (Fig. 3, Table 2). Other teeth were rarely missing.

PAX9 *Dental Phenotype*

The 31 articles reporting *PAX9* mutations included 132 patients and 38 autosomal dominant mutations that occurred in association with isolated dental agenesis (MIM# 604625) (Appendix Table). The number of missing teeth ranged from 2 to 29 (mean, 12.93; Fig. 2A). Hypodontia occurred in 8.33% of patients, whereas oligodontia occurred in 91.67%.

No anomalies were noted in other organs. However, 1 patient had osteogenesis imperfecta due to a *COL1A2* mutation (Wang et al. 2012). Hypotrichosis and gray hair were reported in a family affected by c.59delC, but the authors did not affirm a relationship with the *PAX9* mutation (Mostowska et al. 2013). Some patients were described as having hypercholesterolemia and hyperthyroidism, but it is unclear whether PAX9 deficiency would affect thyroid function (Tallon-Walton et al. 2007). In 1 family, cleft lip and palate were reported in a past generation (Das et al. 2003).

Agenesis affected mainly posterior teeth: $_{max}$Mo3 (93.44%), $_{mand}$Mo3 (88.84%), $_{max}$Mo2 (75.76%), and $_{mand}$Mo2 (76.89%). For the first molars and second premolars, a marked difference was noted between the maxilla and mandible: $_{max}$Mo1(67.80%) and $_{max}$PM2 (60.61%) were more often absent than mandibular ones ($_{mand}$Mo2 [34.85%], $_{mand}$PM2 [40.53%]). Anterior teeth were less often affected by agenesis except for the mandibular central incisors (Fig. 3, Table 2).

AXIN2 *Dental Phenotype*

Five articles described 19 patients with 9 heterozygous mutations in the *AXIN2* gene (Appendix Table). Of those 19 patients, 7 (36.84%) had isolated oligodontia and 12 (63.16%) had syndromic oligodontia (MIM#608615) (Table 1). Oligodontia was associated with complete penetrance of colorectal cancer in a single 4-generation Finnish family. Patients with normal dentition did not have cancer (Marvin et al. 2011).

The number of missing teeth for those with the *AXIN2* mutation ranged from 7 to 29 (mean, 14.7) (Fig. 2B). Hypodontia was not reported. In this patient group, the most prevalent missing teeth were $_{max}$PM2 (78.95%), $_{mand}$PM2 (81.58%), $_{max}$Mo3 (76.92%), $_{mand}$Mo3 (66.67%), $_{mand}$CI (66.67%), $_{max}$LI (57.89%), and $_{mand}$LI (57.89%). Less common agenesis was observed for $_{max}$Mo1 (36.84%), $_{mand}$Mo1 (44.74%), and $_{mand}$PM1 (34.21%). Canine and maxillary central incisor agenesis was rare (Fig. 3, Table 2).

EDA *Dental Phenotype*

X-linked *EDA* mutations were reported in 25 articles describing 99 patients and 32 mutations (Appendix Table). Of those 99 patients, 84 had nonsyndromic tooth agenesis (MIM#313500); that is, tooth agenesis in a context described as normal hair

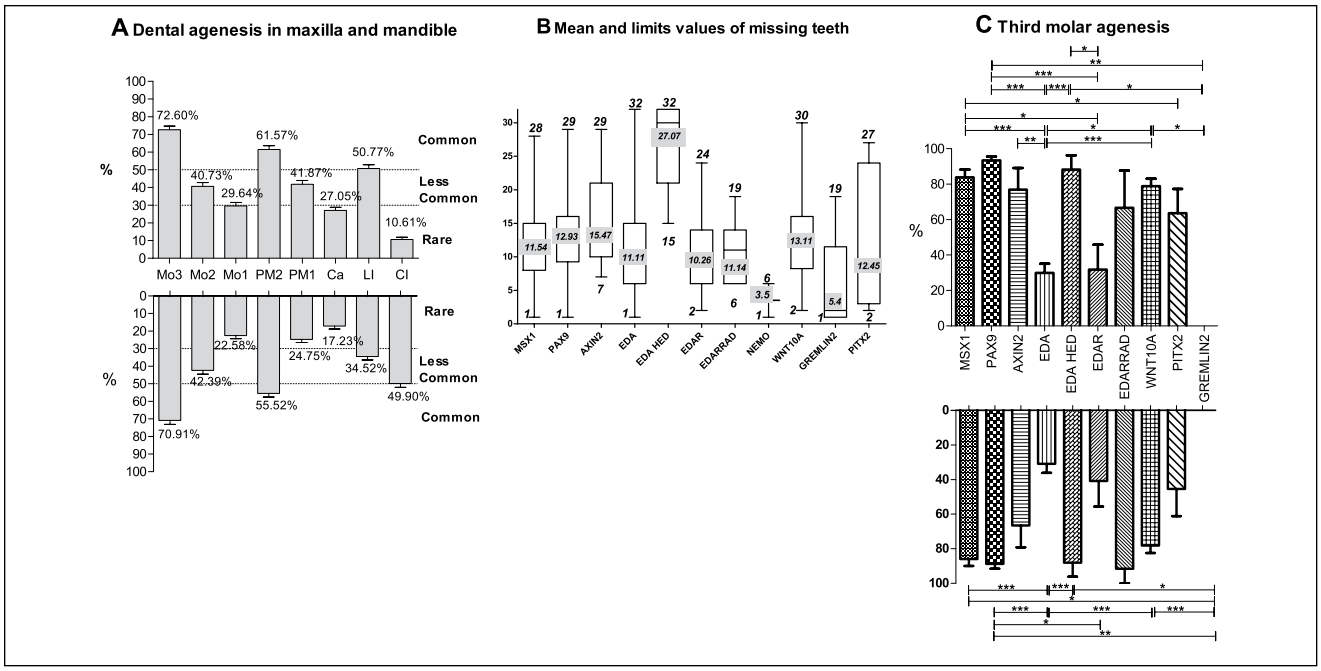

Figure 2. Clinical phenotype analysis of 522 included patients with dental agenesis. (**A**) Percentage of missing teeth from the maxillary (top panel) and mandibular (bottom panel) arches, pooling all patients affected by *MSX1, PAX9, AXIN2, EDA, EDA* (*HED*), *EDAR, EDARADD, NEMO, WNT10A, GREMLIN2*, and *PITX2* gene mutations that define the 3 groups of agenesis (common, less common, and rare). (**B**) Mean number (highlighted in gray) and limit values of missing teeth associated with each gene. (**C**) Dental agenesis of third molars associated with mutations in *MSX1, PAX9, AXIN2, EDA, EDAR, EDARADD, EDA* (*HED*), *PITX2*, and *WNT10A*. Ca, canine; CI, central incisor; LI, lateral incisor; Mo, molar; PM, premolar. $*P \leq 0.05$. $**P \leq 0.001$. $***P \leq 0.0001$.

density, body hair, eyes, nails, facial appearance, thermal tolerance, sweating, lachrymal secretions, and salivary secretions (Tao et al. 2006; Tarpey et al. 2007; Fan et al. 2008; Han et al. 2008). However, careful examination of patient photos showed that some lacked the lateral one-third of the eyebrow (Tao et al. 2006; Song et al. 2009; Sarkar et al. 2014); had fine, curly hair with hypotrichosis (Tarpey et al. 2007; Lee et al. 2014); had balding at an early age (middle to late 20s); or had thin skin (Mues et al. 2010).

For this group of 84 patients without HED, the number of missing teeth ranged from 0 (in a female carrier) to complete anodontia. The mean percentage of missing teeth was 11.11 (Fig. 2A). Female carriers accounted for 14.28% (12/84) of patients and were missing 0 to 12 teeth (mean, 5.92). Male patients accounted for 85.71% of patients, and their mean number of missing teeth was significantly higher, 11.97. Hypodontia was reported in 19.04% of patients and oligodontia in 80.95%. Agenesis of the permanent teeth was more frequent anteriorly: $_{mand}$CI (76.79%), $_{mand}$LI (76.19%), $_{max}$LI (72.02%), and $_{max}$CI (30.88%). Third molars were less often missing (29.87% of $_{max}$Mo3, 30.92% of $_{mand}$Mo3). Agenesis was rarely observed for other molars (Fig. 3, Table 2).

On the other hand, 15 patients were reported with HED or EDA (MIM#305100) (Appendix Table). Patients had the typical phenotype of hypotrichosis, hypohidrosis, and hypodontia or severe oligodontia (Table 1). There was a high rate of missing teeth (mean, 27.66), with a mean greater than 50% agenesis for each tooth. The teeth least likely to be missing were the maxillary central incisors, but they were still missing in 41.18% of patients (Table 2).

EDAR/EDARADD *Dental Phenotype*

Three articles reported 6 heterozygous *EDAR* mutations in association with isolated dental agenesis in 27 patients (Appendix Table). These patients were missing a mean of 10.22 teeth (range, 2–24) (Fig. 2A). Hypodontia occurred in 18.52% of patients, whereas oligodontia occurred in 81.48%. Common agenesis was observed for $_{max}$LI (98.15%), $_{mand}$LI (75.93%), and $_{mand}$CI (74.07%), while $_{max}$CI was present in almost all patients. Less commonly, agenesis was observed for premolars, canines, and third molars (Fig. 3, Table 2). Second molars, first molars, and central maxillary incisors were rarely missing.

Three articles reported 3 heterozygous *EDARADD* gene mutations associated with oligodontia in 7 patients. Patients were missing a mean of 11.14 teeth (range, 6–19; Fig. 2A). Common agenesis was reported for $_{mand}$Mo3 (91.67%), $_{mand}$PM2 (85.71%), $_{max}$PM2 (78.57%), $_{max}$Mo3 (66.67%) (Fig. 3, Table 2).

WNT10A *Dental Phenotype*

Twelve articles reported 24 mutations of *WNT10A* in 140 patients (Appendix Table). Homozygous *WNT10A* gene mutations were associated with Schöpf-Schulz-Passarge syndrome (SSPS, MIM#224750) (Bohring et al. 2009). Heterozygous or homozygous mutations were associated with odonto-onychodermal dysplasia (OODD, MIM#257980) and isolated missing teeth (Table 1). Coexistence of 2 of 3 phenotypes was reported in patients from the same family (Wedgeworth et al. 2011). The c.810C>A (Tziotzios et al. 2014) and c.1066G>T (Kantaputra

Table 1. Clinical Phenotypes of Main Syndromes Associated with Dental Agenesis.

Gene	MIM Phenotype	Name of Disease	Clinical Phenotype Associated with Dental Agenesis
MSX1	189500	Witkop syndrome	Dystrophic nails, easily broken
	194190	Wolf-Hirschhorn syndrome	Craniofacial abnormalities including, microcephaly, maxillary hypoplasia, hypertelorism, high nasal bridge with a characteristic Greek warrior helmet appearance, oral clefts
	608874	Nonsyndromic cleft lip and palate	Oral cleft
AXIN2	608615	Oligodontia-colorectal cancer syndrome	Multiple colorectal polyps
			Adenoma
			Colorectal cancer
EDA	305100	Hypohidrotic ectodermal dysplasia (HED)	Hypohidrosis
EDAR	129490		Hypotrichosis
EDARADD	224900		Fine, curly hair
	614940		Eczema
	614941		Lack of eyebrows
			Nail dystrophy
			Body hair decrease
			Dry skin
NEMO	308300	Incontinentia pigmenti (IP)	Skin lesions along Blaschko's lines
			Occular anomalies
			Central nervous system anomalies
			Abnormal hair
			Abnormal nails
			Nipple and breast anomalies
WNT10A	224750	Schöpf-Schulz-Passarge syndrome (SSPS)	Eyelid cysts
			Slow hair growth
			Nail dystrophy
			Increased sweating over the scalp, palms, and soles
			Palmoplantar keratodermia
			Risk of malignant skin cancer
			Smooth tongue
	257980	Odonto-onycho-dermal dysplasia (OODD)	Nail dystrophy
			Palmoplantar keratodermia
			Hypotrichosis
GREMLIN2	NA	Oligodontia, short stature, mitral valve prolapse	Dry skin
			Slow hair growth
			Fine hair
			Hyperpigmentation around eyes
PITX2	180500	Axenfeld-Rieger syndrome, type 1	Posterior embryotoxon
			Hypoplasia or malformation of the iris
			Anterior synechiae
			Corectopia, polycoria
			Risk for glaucoma
			Umbilical hernia
			Hearing loss
			Heart anomalies
LTBP3	601216	Dental anomalies and short stature	Increased bone density
			Short stature
			Platyspondyly
			Amelogenesis imperfecta

NA, not available.

et al. 2014) mutations have been reported in both isolated and syndromic dental agenesis (SSPS and OODD). Two hotspot mutations (c.321C>A, c.682T>A) are highlighted.

The number of missing teeth ranged from 2 to 30 (mean, 13.11) (Fig. 2A). Of 140 patients, 11 (7.86%) had hypodontia and 129 (92.14%) had oligodontia. Maxillary central incisors were the teeth least frequently affected by agenesis (3.93%). Once again, the last teeth of a group (LI, PM2, Mo3) were more often affected: $_{max}$Mo3 (78.89%), $_{mand}$Mo3 (78.26%), $_{mand}$PM2 (71.43%), and $_{max}$LI (59.29%) (Table 2). Rare missing teeth were $_{max}$Mo1 (16.43%), $_{mand}$Mo1 (13.21%), and $_{mand}$Ca (23.21%) (Fig. 3, Table 2). The c.637G>A mutation was associated with isolated maxillary canine agenesis (Kantaputra et al. 2014).

Correlation of Genetic Mutation with Dental Agenesis Profile: The Nature of Missing Teeth and Gene Mutations

Maxillary central incisor agenesis was associated with *EDA* mutation in 35.71% of patients, compared to 10.53% of patients

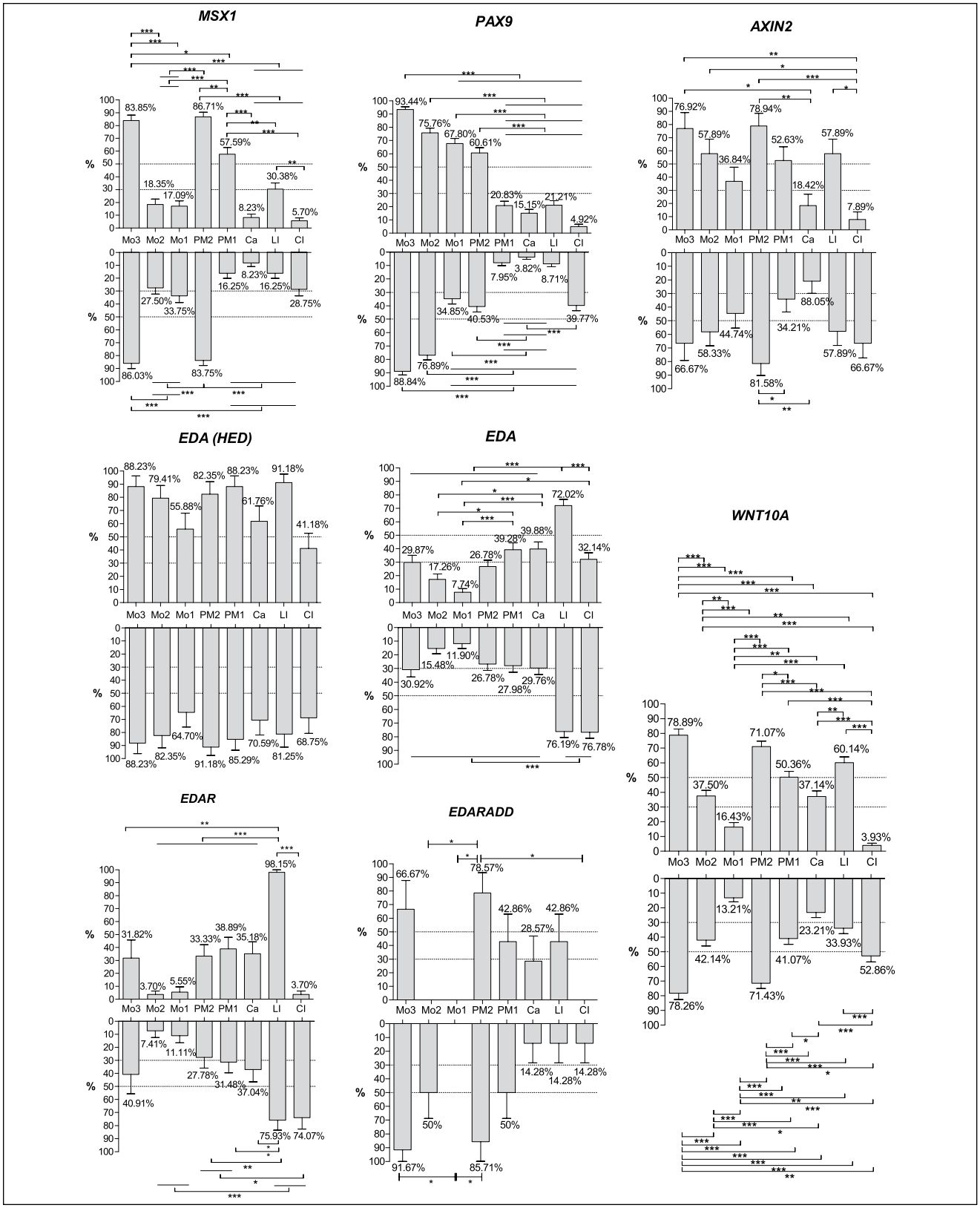

Figure 3. Percentage of missing teeth from the maxillary and mandibular arches, pooling right and left sides, of all patients affected by *MSX1*, *PAX9*, *AXN2*, *EDA*, *EDA* (*HED*), *EDAR*, *EDARADD*, and *WNT10A* gene mutations. Extensive variation in the pattern of missing teeth was observed, highlighting pathognomonic tooth agenesis for candidate gene diagnosis: molar agenesis is linked to *PAX9* mutation, and incisor agenesis is more frequent in cases of *EDA* and *EDAR* mutation. Ca, canine; CI, central incisor; LI, lateral incisor; Mo, molar; PM, premolar. *$P \leq 0.05$. **$P \leq 0.001$. ***$P \leq 0.0001$.

Table 2. Number and Percentage of Missing Teeth and Number and Percentage of Patients Affected by Each Mutated Gene Analyzed, *MSX1, PAX9, AXN2, EDA, EDAR, EDARADD, NEMO, WNT10A, GREMLIN2*, and *PITX2*.

	No. and Percentage of Patients and Missing Teeth	Mo3	Mo2	Mo1	PM2	PM1	Ca	LI	CI
Maxillary									
MSX1	No. of described patients	65	79	79	79	79	79	79	79
	No. of affected patients	56	16	15	70	50	9	29	6
	Total missing teeth	109	29	27	137	91	13	48	9
	% of missing teeth	83.85	18.35	17.09	86.71	57.59	8.23	30.38	5.70
	% of affected patients	86.15	20.25	18.99	88.61	63.29	11.39	36.71	7.59
PAX9	No. of described patients	122	132	132	132	132	132	132	132
	No. of affected patients	116	103	97	89	31	26	32	5
	Total missing teeth	228	200	179	160	55	40	56	13
	% of missing teeth	93.44	75.76	67.80	60.61	20.83	15.15	21.21	4.92
	% of affected patients	95.08	78.03	73.48	67.42	23.48	19.70	24.24	3.79
AXIN2	No. of described patients	13	19	19	19	19	19	19	19
	No. of affected patients	10	12	8	15	12	4	12	2
	Total missing teeth	20	22	14	30	20	7	22	3
	% of teeth missing	76.92	57.89	36.84	78.95	52.63	18.42	57.89	7.89
	% of patients affected	76.92	63.16	42.11	78.95	63.16	21.05	63.16	10.53
EDA	No. of described patients	77	84	84	84	84	84	84	84
	No. of affected patients	23	16	8	25	36	36	64	30
	Total missing teeth	46	29	13	45	66	67	121	54
	% of teeth missing	29.87	17.26	7.74	26.79	39.29	39.88	72.02	32.14
	% of patients affected	29.87	19.05	9.52	29.76	42.86	42.86	76.19	35.71
EDA (*HED*)	No. of described patients	11	11	11	11	11	11	11	11
	No. of affected patients	11	10	7	9	11	8	11	7
	Total missing teeth	22	19	14	18	22	15	20	12
	% of teeth missing	100.00	86.36	63.64	81.82	100.00	68.18	90.91	54.55
	% of patients affected	100.00	90.91	63.64	81.82	100.00	72.73	100.00	63.64
EDAR	No. of described patients	11	27	27	27	27	27	27	27
	No. of affected patients	4	2	2	10	12	10	27	2
	Total missing teeth	7	2	3	18	21	19	53	2
	% of teeth missing	31.82	3.70	5.56	33.33	38.89	35.19	98.15	3.70
	% of patients affected	36.36	7.41	7.41	37.04	44.44	37.04	100.00	7.41
EDARADD	No. of described patients	6	7	7	7	7	7	7	7
	No. of affected patients	4	0	0	6	3	2	3	0
	Total missing teeth	8	0	0	11	6	4	6	0
	% of teeth missing	66.67	0.00	0.00	78.57	42.86	28.57	42.86	0.00
	% of patients affected	66.67	0.00	0.00	85.71	42.86	28.57	42.86	0.00
NEMO	No. of described patients	0	2	2	2	2	2	2	2
	No. of affected patients	0	0	0	0	0	0	1	0
	Total missing teeth	0	0	0	0	0	0	2	0
	% of teeth missing	NA	0.00	0.00	0.00	0.00	0.00	50.00	0.00
	% of patients affected	NA	0.00	0.00	0.00	0.00	0.00	50.00	0.00
WNT10A	No. of described patients	90	140	140	140	140	140	140	140
	No. of affected patients	73	60	26	104	81	59	91	6
	Total missing teeth	142	105	46	199	141	104	166	11
	% of teeth missing	78.89	37.50	16.43	71.07	50.36	37.14	59.29	3.93
	% of patients affected	81.11	42.86	18.57	74.29	57.86	42.14	65.00	4.29
GREMLIN2	No. of described patients	4	5	5	5	5	5	5	5
	No. of affected patients	0	2	0	1	1	1	3	0
	Total missing teeth	0	3	0	2	2	2	6	0
	% of teeth missing	0.00	30.00	0.00	20.00	20.00	20.00	60.00	0.00
	% of patients affected	0.00	40.00	0.00	20.00	20.00	20.00	60.00	0.00
PITX2	No. of described patients	11	11	11	11	11	11	11	11
	No. of affected patients	8	5	5	7	3	4	9	3
	Total missing teeth	14	9	9	14	6	6	18	5
	% of teeth missing	63.64	40.91	40.91	63.64	27.27	27.27	81.82	22.73
	% of patients affected	72.73	45.45	45.45	63.64	27.27	36.36	81.82	27.27
Mandible									
MSX1	No. of described patients	68	80	80	80	80	79	80	80
	No. of affected patients	60	24	29	69	15	8	15	24
	Total missing teeth	117	44	54	134	26	13	26	46
	% of missing teeth	86.03	27.50	33.75	83.75	16.25	8.23	16.25	28.75
	% of affected patients	88.24	30.00	36.25	86.25	18.75	10.13	18.75	30.00

(continued)

Table 2. (continued)

	No. and Percentage of Patients and Missing Teeth	Mo3	Mo2	Mo1	PM2	PM1	Ca	LI	CI
PAX9	No. of described patients	121	132	132	132	132	131	132	132
	No. of affected patients	109	105	52	59	13	6	15	64
	Total missing teeth	215	203	92	107	21	10	23	105
	% of missing teeth	88.84	76.89	34.85	40.53	7.95	3.82	8.71	39.77
	% of affected patients	90.08	79.55	39.39	44.70	9.85	4.58	11.36	48.48
AXIN2	No. of described patients	15	18	19	19	19	19	19	18
	No. of affected patients	10	13	10	16	9	5	13	13
	Total missing teeth	20	21	17	31	13	8	22	24
	% of teeth missing	66.67	58.33	44.74	81.58	34.21	21.05	57.89	66.67
	% of patients affected	66.67	72.22	52.63	84.21	47.37	26.32	68.42	72.22
EDA	No. of described patients	76	84	84	84	84	84	84	84
	No. of affected patients	24	15	11	25	25	29	68	68
	Total missing teeth	47	26	20	45	47	50	128	129
	% of teeth missing	30.92	15.48	11.90	26.79	27.98	29.76	76.19	76.79
	% of patients affected	31.58	17.86	13.10	29.76	29.76	34.52	80.95	80.95
EDA (*HED*)	No. of described patients	11	11	11	11	11	11	11	11
	No. of affected patients	11	10	7	10	11	8	10	9
	Total missing teeth	22	20	13	20	21	16	18	16
	% of teeth missing	100.00	90.91	59.09	90.91	95.45	72.73	81.82	72.73
	% of patients affected	100.00	90.91	63.64	90.91	100.00	72.73	90.91	81.82
EDAR	No. of described patients	11	27	27	27	27	27	27	27
	No. of affected patients	5	2	4	9	11	10	22	20
	Total missing teeth	9	4	6	15	17	20	41	40
	% of teeth missing	40.91	7.41	11.11	27.78	31.48	37.04	75.93	74.07
	% of patients affected	45.45	7.41	14.81	33.33	40.74	37.04	81.48	74.07
EDARADD	No. of described patients	6	6	7	7	7	7	7	7
	No. of affected patients	6	4	0	6	4	1	1	1
	Total missing teeth	11	7	0	12	7	2	2	2
	% of teeth missing	91.67	58.33	0.00	85.71	50.00	14.29	14.29	14.29
	% of patients affected	100.00	66.67	0.00	85.71	57.14	14.29	14.29	14.29
NEMO	No. of described patients	0	2	2	2	2	2	2	2
	No. of affected patients	0	0	0	1	0	0	1	1
	Total missing teeth	0	0	0	1	0	0	2	2
	% of teeth missing	NA	0.00	0.00	25.00	0.00	0.00	50.00	50.00
	% of patients affected	NA	0.00	0.00	50.00	0.00	0.00	50.00	50.00
WNT10A	No. of described patients	92	140	140	140	140	140	140	140
	No. of affected patients	73	68	21	106	66	36	54	77
	Total missing teeth	144	118	37	200	115	65	95	148
	% of teeth missing	78.26	42.14	13.21	71.43	41.07	23.21	33.93	52.86
	% of patients affected	79.35	48.57	15.00	75.71	47.14	25.71	38.57	55.00
GREMLIN2	No. of described patients	4	5	5	5	5	5	5	5
	No. of affected patients	0	1	0	2	0	1	2	1
	Total missing teeth	0	2	0	3	0	2	3	2
	% of teeth missing	0.00	20.00	0.00	30.00	0.00	20.00	30.00	20.00
	% of patients affected	0.00	20.00	0.00	40.00	0.00	20.00	40.00	20.00
PITX2	No. of described patients	11	11	11	11	11	11	11	11
	No. of affected patients	5	2	2	9	3	2	4	4
	Total missing teeth	10	4	3	15	5	4	8	7
	% of teeth missing	45.45	18.18	13.64	68.18	22.73	18.18	36.36	31.82
	% of patients affected	45.45	18.18	18.18	81.82	27.27	18.18	36.36	36.36
	% of patients affected	45.45	18.18	18.18	81.82	27.27	18.18	36.36	36.36

Data were tabulated for all teeth from the maxillary and mandibular arches, pooling the right and left sides.
Ca, canine; CI, central incisor; LI, lateral incisor; Mo, molar; NA, not available; PM, premolar.

with *AXIN2*, 4.29% with *WNT10A*, 7.59% with *MSX1*, and 3.79% with *PAX9* mutations (Appendix Fig. 2). Maxillary lateral incisors were rarely affected by *PAX9* or *MSX1* mutations (21.21% and 30.38% of missing teeth, respectively); therefore, *EDA* and *EDAR* mutations were associated with 72.02% and 98.15% of missing maxillary lateral incisors, respectively.

Canine agenesis was similar in the maxillary and mandibular arches and more often absent in association with *EDA* and

WNT10A mutations compared to other gene mutations (Appendix Fig. 2).

First premolar agenesis was less common than second premolar agenesis for mutations in all genes except *EDA* (Fig. 4, Appendix Fig. 3).

Maxillary and mandibular molar agenesis was common with *PAX9* and *AXIN2* mutations and less common for other gene mutations. A range of molar agenesis rates has been observed for mutated *PAX9, EDA*, and *EDAR* genes. First and second molars were more often absent with *PAX9* mutations and more often present with *EDA* mutations.

Discussion

We performed a systematic review of dental agenesis case reports and aimed at correlating genotypes to the different tooth-specific agenesis phenotypes. Dental agenesis is caused by early developmental arrest at the tooth initiation or morphogenesis stage. Genetic studies on mouse models with dental agenesis have identified a number of transcription factors and signaling molecules such as WNTs, BMPs, FGFs, and nuclear factor (NF)–κB as candidate genes in human isolated and syndromic agenesis (Tucker and Sharpe, 2004). Meanwhile, Mendelian inheritance studies performed on single known or candidate genes and larger sets of genes using next-generation sequencing technologies have identified more than 150 syndromes and 80 genes related to human tooth agenesis (Polder et al. 2004; Yin and Bian 2015). Moreover, there are now a reasonable number of clinical reports in which both tooth agenesis phenotypes and sequenced gene mutations are available to allow exploration of associations, and this is the subject of the present study.

Here, we determined that, except for *PAX9* gene mutations, mutations in all previously described genes led to both isolated and syndromic dental phenotypes. Classically, 2 groups of genes linked to dental agenesis have been described: those associated only with isolated dental agenesis, such as *MSX1, PAX9*, and *AXIN2*, and those associated with syndromic dental agenesis, such as *PITX2* or *TP63*. Recently, a third group has emerged that is involved in both isolated dental agenesis and ectodermal dysplasia, with members such as *EDA, EDAR, EDARADD*, or *WNT10A*. Our analysis showed that the same *MSX1* mutations led to both isolated dental agenesis and oral cleft. Other mutations in the same gene led to syndromic agenesis (Witkop and Wolf-Hirschhorn syndromes). Similarly, *AXIN2* mutations have been described in isolated oligodontia and associated with middle-aged patients with colorectal cancer. Young patients with isolated dental agenesis caused by *AXIN2* mutations may go on to develop cancer during adulthood. On the other hand, ectodermal anomalies are the most frequent signs associated with dental agenesis with a mild phenotype such as eczema, thin skin, external part decrease in eyelids, or smooth nails, which may be misdiagnosed. Indeed, the presence of only 1 or 2 ectodermal signs excludes a diagnosis of ectodermal dysplasia but should be considered an infrasyndromic form. Our study further supports that *WNT10A* and *EDA*/*EDAR*/*EDARADD* are good candidate genes in cases of severe oligodontia with discrete ectodermal anomalies (sweating abnormalities, nail or hair anomalies, palmoplantar hyperkeratosis). These 2 examples highlight how essential the identification of the specific mutation is to direct patients to the appropriate preventive care and to design their follow-up. We hypothesized here that the pattern of agenesis would be indicative of a specific gene mutation.

In dental agenesis, patients do not always show the same pattern of missing teeth. Polder et al. (2004), in a meta-analysis of the prevalence of dental agenesis, established that some tooth types were more often missing than other ones (i.e., second premolar and maxillary lateral incisor). The overall prevalence of agenesis in the maxilla is comparable with those in the mandible. In our study, we showed that the pattern of missing teeth varies according to each mutated gene and does not reflect results of pooled data from the 522 patients (Fig. 2A). Usually, third molar agenesis is excluded from dental agenesis studies because of the high frequency of isolated third molar agenesis in the general population. However, our study showed that including third molar agenesis might be helpful in correlating dental phenotype to genotype. Indeed, *MSX1* and *PITX2* are responsible for third molar and premolar agenesis while *PAX9* mutations result in agenesis of all molars and mandibular central incisors. *EDA* mutations were associated with a high level of incisor agenesis, especially the maxillary central incisor, which is usually the least affected tooth. Interestingly, we also noticed that mutations of genes coding for signaling molecules downstream of EDA produced the same missing tooth pattern as *EDA* mutations. In addition, we showed that for *EDA* mutations, third molars were less likely to be absent than mandibular incisors. Indeed, the homeobox genes *PITX2, MSX1, AXIN2*, and *PAX9* encode transcription factors involved in embryonic development, notably the initiation and morphogenetic stages of tooth development. Their expressions and functions were redundant, recurrent with some feedback loop. For example, epithelial expression of Bmp4 and mesenchymal expression of Pax9 regulate *Msx1* expression in mesenchymal cells, which in turn regulate *Bmp4* expression in epithelial cells (Appendix Fig. 4). Both *Msx1* and *Pax9* knockout mice showed arrest of tooth development, accompanied by reduced Bmp4 expression (Satokata and Maas 1994; Peters et al. 1998). *Msx1*+/–, *Pax9*+/– (double heterozygous) mice lacked mandibular incisors and third molars, a phenotype that was partially rescued by Bmp4 overexpression in transgenic mice (Nakatomi et al. 2010). Others studies show that, in the presumptive incisor field, Bmp4 is expressed in oral epithelium, triggering *Msx1* and *Msx2* expression in the underlying mesenchyme, whereas in the presumptive molar field, *Pitx2* is expressed and induces *Fgf8* epithelial expression, which then triggers the expression of mesenchymal *Barx-1* and *Dlx2*. This scenario is supported by the observation that a molar developed instead of an incisor when *Bmp4* was inhibited (Tucker et al. 1998). Sharpe and colleagues proposed in mice a dental homeocode in which the anterior part of the mandible does not express the same combination of homeogenes as the posterior part (Tucker and Sharpe 2004). The patterns of dental agenesis described in this

human study may reflect the expression of the dental homeocode in humans (Davideau et al. 1999). Some tooth types (canine, premolar) cannot be analyzed in mice, so this study brings new perspectives to understanding the molecular pathways implicated in human odontogenesis. Differences between humans and rodents might also be associated with the importance of the incisors among rodents, which are less essential for omnivores such as humans. Furthermore, rodents have only one dentition, and thus temporary dentition can only be studied in appropriate organisms such as humans.

The average number of missing teeth in *EDA*-mutated patients was lower in the isolated form (11.11) than in HED patients (27.07), who often exhibited anodontia. The *EDA* gene encodes a transmembrane protein implicated in all ectodermal appendage development, such as nail, sweat gland, hair, and teeth. On binding to its receptor EDAR, EDA triggers the intracellular activation of the NF-κB pathway, including presumably EDARADD. Tooth development may require the most amount of EDA compared to any other ectodermal appendage. Indeed, when EDA-deficient pregnant mice were treated with recombinant EDA1, offspring developed ectodermal appendages but not teeth (Srivastava et al. 2001). Mutations impairing interactions of EDA with its receptors contribute to X-linked hypohidrotic ectodermal dysplasia, whereas mutations leading to isolated dental agenesis affect a more specific EDA function, for example, the stability of homotrimers (Song et al. 2009). Female carriers (heterozygotes) present a range of dental agenesis, from a normal number of teeth to hypodontia, which is explained by the expression of the normal allele on the noninactivated X chromosome (Tarpey et al. 2007). In addition, an experimental study showing different levels of reduction of Pax9 expression in transgenic mice resulted in a proportionate increase in the number of missing teeth, suggesting that a minimal level of expression is required to initiate dental formation along an anteroposterior gradient (Kist et al. 2005). This was confirmed in humans. Four patients through 3 generations with a nonsense mutation (p.Ile207fs) of PAX9 showed the same severe phenotype with 18 missing teeth (molars, premolars, and mandibular central incisors), whereas a missense mutation (p.Gly6Arg) led to middle oligodontia with 7 missing teeth (third molars, 1 premolar, and both mandibular central incisors). The nature of mutations and their consequences for protein function are sufficiently well known to explain the variability of clinical manifestations. It is clear that some mutations lead to the same tooth agenesis phenotype. For example, Mostowska et al. (2015) showed that 2 *WNT10A* variants (p.Arg113Cys and p.Phe228Ile) may be etiological mutations underlying maxillary lateral incisor agenesis (MLIA). Moreover, polymorphisms of *PAX9, EDA, WNT10A*, and *MSX1* have been reported in dental agenesis patients without other mutations. Polymorphisms were found in either the heterozygous or homozygous state and were often multiple in the same patient. For example, polymorphisms IVS2-41A>G, IVS2-109G>C, or IVS3-40G>A of *PAX9* were reported in patients with oligodontia (Pawlowska et al. 2010). For *WNT10A*, it has been shown that the G allele of the intronic variant rs2385199 is associated with increased susceptibility to MLIA (Alves-Ferreira et al. 2014).

Taken together, animal experiments and the present study showed that several physiological processes define tooth-type identity: existence of a minimal level of gene/protein expression in a regional gradient, redundant function of signaling molecules, sequential epithelial-mesenchymal interactions, and specific combinations of homeogene expression differing from one area to another. Each tooth could be considered the product of a unique combination and dosage of all genes implicated in dental morphogenesis. We may hypothesize that aberrant expression of one of these genes can be compensated by the expression of other genes, which may explain why only certain teeth are missing. In terms of a single mutated gene, the most prevalent missing tooth could be considered the tooth with the highest susceptibility to the loss of that gene product. The importance of the mutation leads first to agenesis of this susceptible tooth. Biallelic mutations lead to higher numbers of missing teeth (e.g., *WNT10A*). In addition, when 2 different genes are mutated in the same patient, the phenotype of missing tooth types changes further. Some other mechanisms such as DNA methylation and epigenetic factors were recently suggested to be involved as well in tooth agenesis and need to be further explored (Wang et al. 2016; Li et al. 2018).

Conclusion

Our study revealed that the pattern of missing teeth, including third molars, might be useful in directing molecular research and appropriate patient care. Dental agenesis should be considered a clinical sign of a possible underlying syndrome and not only as an isolated disease. Indeed, syndromic disorders associated with dental abnormalities range from discrete ectodermal anomalies to more severe pathologies like colorectal polyps and ocular glaucoma. Geneticists should exploit dental exam findings as an accessible and useful tool to predict mutated candidate genes. Correlations between genotype and phenotype established for the first time in dental agenesis bring new perspectives to dental research.

Author Contributions

B.P. Fournier, contributed to conception, design, data analysis, and interpretation, drafted and critically revised the manuscript; M.H. Bruneau, contributed to conception, design, and data acquisition, drafted and critically revised the manuscript; S. Toupenay, contributed to conception and data interpretation, drafted and critically revised the manuscript; S. Kerner, contributed to conception and data acquisition, drafted and critically revised the manuscript; A. Berdal, V. Cormier-Daire, S. Hadj-Rabia, contributed to data interpretation, drafted and critically revised the manuscript; A.E. Coudert, contributed to data analysis and interpretation, drafted and critically revised the manuscript; M. de La Dure-Molla, contributed to conception, design, data acquisition, analysis, and interpretation, drafted and critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of the work.

Acknowledgments

The authors received no financial support and declare no potential conflicts of interest with respect to the authorship and/or publication of this article.

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