Disturbances of dental development distinguish oligodontia-ectodermal dysplasia from isolated oligodontia

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ABSTRACT

Objective: In this study we aimed to investigate phenotypic differences in dental development between isolated oligodontia and oligodontia as part of ectodermal dysplasia (ED).
Methods: A total of 129 patients diagnosed with isolated oligodontia and 22 patients with oligodontia as part of ED were eligible for this study. The phenotype of dental development was assessed for the frequency of missing a certain tooth, dental age, development of each present tooth, abnormal size and abnormal shape of teeth.
Results: Patients with oligodontia-ED distinctively missed more frequently central incisors and second molars in both jaws and lateral incisors in the mandible compared to patients with isolated oligodontia ($p<0.05$). Oligodontia-ED was associated with delayed development of the permanent dentition (β, -0.10, 95% CI: -0.17, -0.03). Specifically, the development of the maxillary teeth: right central incisor, right lateral incisor, right second premolar and left second premolar were approximately 2-4 stages delayed. Meanwhile the development of the left mandibular second premolar was approximately 3 stages delayed in development. Abnormal shape of teeth was approximately seven times more evident in patients with oligodontia-ED than in patients with isolated oligodontia (OR 6.54; 95% CI: 2.34, 18.28). In contrast, the abnormal size of teeth was not a distinctive characteristic for oligodontia-ED.
Conclusions: Oligodontia-ED distinguishes from isolated oligodontia by more agenetic second molars and delayed development of the present teeth, especially of maxillary teeth. Furthermore, the abnormal shape of incisors and canines in a patient with oligodontia can indicate an ectodermal dysplasia syndrome.
Clinical relevance: This approach could facilitate the differential diagnosis between isolated oligodontia and oligodontia-ED.

4.2.1 INTRODUCTION

Dental agenesis is the most common anomaly of dental development in humans with an incidence that varies from 2.6% to 11.3% in different populations [1-6]. According to the number of missing teeth, dental agenesis is classified as hypodontia, oligodontia and anodontia [7-9]. Oligodontia is the condition of missing congenitally 6 or more teeth excluding the third molars [9-11]. It is observed approximately in 0.14% of the general population [12] and specifically in the Dutch population the prevalence of oligodontia is 0.08% [13]. Based on the genetic evidence, oligodontia is caused by alterations of independent genes or genetic linkages that affect early developmental processes of teeth leading to specific phenotypes [14]. Although oligodontia is usually presented as an isolated trait (OMIM 616724), it can also be part of a syndrome [15]. As a non-isolated trait, oligodontia is manifested in more than 120 syndromes and quite often it can be the initial sign in diagnosing a patient with a related syndrome [16]. Ectodermal dysplasia (ED) (OMIM 305100) is the most common group of syndromes associated with oligodontia [17]. ED is characterized by abnormal development of two or more ectodermal structures such as hair, teeth, skin, nails, craniofacial complex, salivary glands, digits etc. Being part of a syndrome, oligodontia presents an extensive phenotype including various dental and craniofacial malformations that require special treatment by an interdisciplinary team of orthodontists, maxillofacial surgeons and prosthodontists [16,18]. Genes play an important role in the occurrence of oligodontia and other disturbances of dental development. Particularly, *MSX1*, *PAX9*, *AXIN2*, *EDA*, *EDAR*, *EDARADD* and *WNT10A* variants, responsible for isolated oligodontia and oligodontia-ED are known to be associated with an aberrant development of the dentition as well, reflected on the structure, number, position and morphology of the teeth [19,11,20-24]. Disturbances of dental development that characterize oligodontia refer to the delay of dental development [25], abnormal size (reduced size and short roots of teeth) [26] and abnormal shape (taurodontism, conical shape) of teeth [27,28]. However, whether the abnormal features affecting teeth can be discriminative between isolated oligodontia and oligodontia-ED remains a question as the literature doesn't share enough insight on the complete phenotype of dental development in the both conditions. Hence, the aim of this study is to assess the phenotypic differences in dental development between patients with isolated oligodontia and non-isolated oligodontia as part of ectodermal dysplasia.

4.2.2 MATERIALS AND METHODS

4.2.2.1 Study population

The participants in this cross-sectional study were referred from 1989-2016 to two medical centers and one private orthodontic center: Erasmus University Medical Center, Radboud University Nijmegen Medical Center and Orthodontiepraktijk Heerenveen. A total of 182 patients were detected with oligodontia (6 or more missing teeth, excluding third molars) and presence of a dental panoramic radiograph (DPR) aged between 6 to 18 years old. Thirty-one patients detected with syndromic oligodontia such as part of Down syndrome, clefts or

other rare syndromes, were excluded from this investigation. The 151 patients (74 females and 77 males) included in the study with a median age of 11.30 years (75% range; 8.80-14.18 years) and born between 1975-2010 fulfilled the diagnosis selection criteria and were classified as manifesting isolated oligodontia (N = 129) or oligodontia as part of ectodermal dysplasia (N = 22). The group of patients manifesting isolated oligodontia was used as the reference group. The utilization of DPRs is in accordance with the general treatment protocol, in respect to the Medical Ethical Committee legislation (MEC-2017-190).

4.2.2.2 The assessment of oligodontia

Oligodontia was assessed by clinical examination from the dentist or other dental professional and also by detection in DPRs. A tooth was classified as missing when no sign of formation or calcification was shown in the DPR.

4.2.2.3 The assessment of ectodermal dysplasia

During the physical examination, patients identified with two or more abnormal features of ectoderm (skin, hair, nails and sweat glands) were referred to the clinical geneticist. The genetic test confirmed the diagnosis of ectodermal dysplasia. Informed consents were obtained from the patients or parents.

4.2.2.4 The assessment of dental development

Dental development was defined from each available DPR using the Demirjian method [29]. One experienced examiner (B. D) determined one of the eight developmental stages (A, B, C, D, E, F, G and H) for each present tooth in all quadrants. Dental age was calculated for each patient referring to the stages of development of teeth in the left quadrant as follows. In order to estimate the developmental stage of the missing teeth, a combined method was applied [30]. This method consists of assessing the stage of development for a missing tooth in the lower left quadrant from the corresponding right mandibular tooth or from a corresponding maxillary tooth if the tooth was missing in both sides of the mandible. In case no corresponding tooth was present, regression equations developed by Nystrom et al. were applied [31]. These equations take into account the development of the remaining teeth in the lower left quadrant, age and sex of the patient to calculate dental age. Obtained stages of dental development were used to calculate the dental maturity score by summing up the weighted scores given to every tooth of the lower left quadrant [32]. Finally, the Dutch dental age standard tables for boys and girls were used to convert the dental maturity score into dental age [32]. Due to non-normal distribution, dental age was firstly log transformed and further used in the statistical analysis. To obtain a better approach of dental development, additional measurements were performed. Abnormal shape of teeth (taurodontism, conical tooth shape, notched incisors) and abnormal size of teeth (microdontia, thin and short roots anomalies) were noted when detected in a DPR and intraoral picture. To control for possible confounders, dental fillings as a proxy of dental caries were noted as well.

4.2.2.5 Statistical analysis

The difference in the frequency of missing a certain tooth between isolated oligodontia and oligodontia-ED patients was tested using the t-test. The difference in dental age between isolated oligodontia and oligodontia-ED was investigated using the linear regression analysis in two consecutive models. Model 1 was adjusted only for age. Model 2 was additionally adjusted for the number of missing teeth and number of filled teeth. The difference in the development of each present maxillary and mandibular tooth between isolated oligodontia and non-isolated oligodontia (ED) was analyzed using one ordinal regression model, adjusted for age, sex, number of missing teeth and number of filled teeth. The same analysis was performed to investigate whether the agenesis of a certain tooth influenced the development of its correspondent in the other jaw. The difference in the abnormal shape of teeth (presence of shape abnormalities or not) between isolated oligodontia and oligodontia-ED was investigated using the binary logistic regression analysis in two consecutive steps. Model 1 was adjusted for age and sex. Model 2 was additionally adjusted for the number of missing teeth and number of filled teeth. The same analysis was performed to study the difference in the abnormal size of teeth (presence of size abnormalities or not) between isolated oligodontia and oligodontia-ED. All statistical analyses were performed using statistical software Statistical Package for Social Sciences version 21.0 (SPSS Inc. Chicago, IL, USA).

4.2.3 RESULTS

4.2.3.1 General Characteristics

The general description of the study population is presented in Table 4.2.1.

The difference between the chronological age and dental age was 1.02 years in patients with isolated oligodontia and 2.88 years in patients with ED. Patients with oligodontia-ED had statistically significantly lower dental age, more missing teeth and were more frequently

Table 4.2.1. General characteristics of the study population (N = 151)

	Isolated Oligodontia	**Non-Isolated Oligodontia**	
	Reference Group (N = 129)	Ectodermal Dysplasia (N = 22)	p-value
Age	11.32 (8.81-14.05)	10.98 (7.19-14.51)	0.918
Sex (N; %)			0.278
Females	65 (50.0)	9 (41.0)	
Males	64 (50.0)	13 (59.0)	
Number of missing teeth	10 (6 - 17)	14 (6 - 22)	*<0.001*
Dental age	10.30 (7.55 -12.48)	8.10 (5.40 - 11.56)	*0.012*
Abnormal size of teeth (N; %)	24 (18.6)	7 (31.8)	0.130
Abnormal shape o teeth (N;%)	22 (17.1)	14 (63.6)	*<0.001*
Number of filled teeth	0 (0 - 2)	0 (0 - 0)	0.876

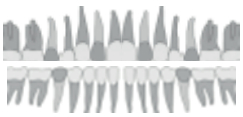
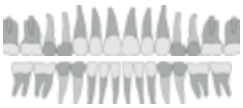
Abbreviations: N- number of participants; Values are percentages for two-categorical variables, or medians (75% range) for ordinal and continuous variables with a skewed distribution Differences were tested using the Kruskal-Wallis Non-Parametric test for continuous variables and t-test for categorical variables; p<0.05 is considered statistically significant and presented in italic font

detected with abnormal shape of teeth than patients with isolated oligodontia. There was no difference in age, gender, abnormal size of teeth and number of filled teeth between the ED patients and isolated oligodontia patients.

4.2.3.2 Patterns of Oligodontia

The frequency of oligodontia patterns is presented in Table 4.2.2, whereas the distribution of missing teeth is presented in Table S4.2.1.

Table 4.2.2. The frequency of oligodontia patterns

Isolated Oligodontia		TAC	Missing Teeth (FDI)	Illustration	N (%)
	Maxilla	48	15, 14, 24, 25		12 (9.3)
		52	15, 14, 12, 22, 24, 25		13 (10.1)
		The others			104 (80.6)
	Mandible	32	45, 35		14 (10.9)
		48	45, 44, 34, 35		13 (10.1)
		The others			102 (79.0)
	Overall dentition	68	15, 12, 22, 25, 45, 35		5 (3.9)
		96	15, 14, 24, 25 45, 44, 34, 35		5 (3.9)
		The others			119 (92.2)
Oligodontia- ED		**TAC**	**Missing Teeth (FDI)**	**Illustration**	**N** (%)
	Maxilla	52	15, 14, 12, 22, 24, 25		2 (9.1)
		180	17, 15, 14, 12, 22, 24, 25, 27		2 (9.1)
		The others			18 (81.8)
	Mandible	6	42, 41, 31, 32		3 (13.6)
		182	47, 45, 44, 42, 41, 31, 32, 34, 35, 37		2 (9.1)
		The others			17 (77.3)

Abbreviations: TAC-score (tooth agenesis code); FDI- World Dental Federation two-digit tooth notation; ED- ectodermal dysplasia; crown of the missing teeth are illustrated in dark grey color (Tan et al. 2011); Patterns that were less frequent are presented as 'the others'; patterns that were present only in one patient are not presented

Isolated oligodontia: The lower second premolars (35, 78.3%; 45, 74.4%), the upper second premolars (15, 72.1%; 25, 69.0%) and the upper lateral incisors (12, 65.9%; 22, 64.3%) were most frequently missing. The upper central incisors (11, 31%; 21, 3.9%), the lower first molars (36, 10.9%; 46, 11.6%) and the upper first molars (16, 14.7%; 26, 12.4%) were less frequently missing.

Oligodontia-ED: The lower central incisors (31, 81.2%; 41, 81.8%), second premolars (15, 68.2%; 25, 68.2%; 35, 68.2%; 45, 72.7%), second molars (17, 72.7%; 27, 68.2%; 37, 68.2%; 47, 68.2%), lateral incisors (12, 63.6%; 22, 72.7%; 32, 63.6%; 42, 68.2%) were most frequently missing. The upper first molars (16, 13.6%; 26, 13.6%) and lower canines (33, 18.2%; 43, 13.6%) were less frequently missing. The frequency of missing the central incisors ($p<0.01$), the lower lateral incisors ($p<0.01$) and the second molars ($p<0.05$) was statistically significantly higher in oligodontia-ED patients compared to isolated oligodontia patients.

4.2.3.3 Differences of dental development in patients with isolated oligodontia and oligodontia-ED

Dental age

As part of ED, oligodontia was associated with a delayed development of the permanent dentition in Model 1 (β, -0.17; 95% CI: -0.25, -0.09). The effect estimate decreased in Model 2 (β, -0.10, 95% CI: -0.17, -0.03), however the association remained statistically significant (Table 4.2.3).

Table 4.2.3. The association between oligodontia-ED and dental age

	Model 1			Model 2		
	β	**95% CI**	**p-value**	**β**	**95% CI**	**p-value**
Ectodermal dysplasia (isolated oligodontia; ref.)	-0.17	-0.25, -0.09	*<0.001*	-0.10	-0.17, -0.03	*0.008*

Abbreviations: β –regression coefficients, CI – confidence interval, ref.-reference; dental age was log-transformed; significant p-values are presented in italic font

Model 1: the association between non-isolated oligodontia and dental age (log-transformed values) is adjusted for age

Model 2: was additionally adjusted for number of missing teeth and number of filled teeth

The development of each present tooth

1-Maxillary teeth

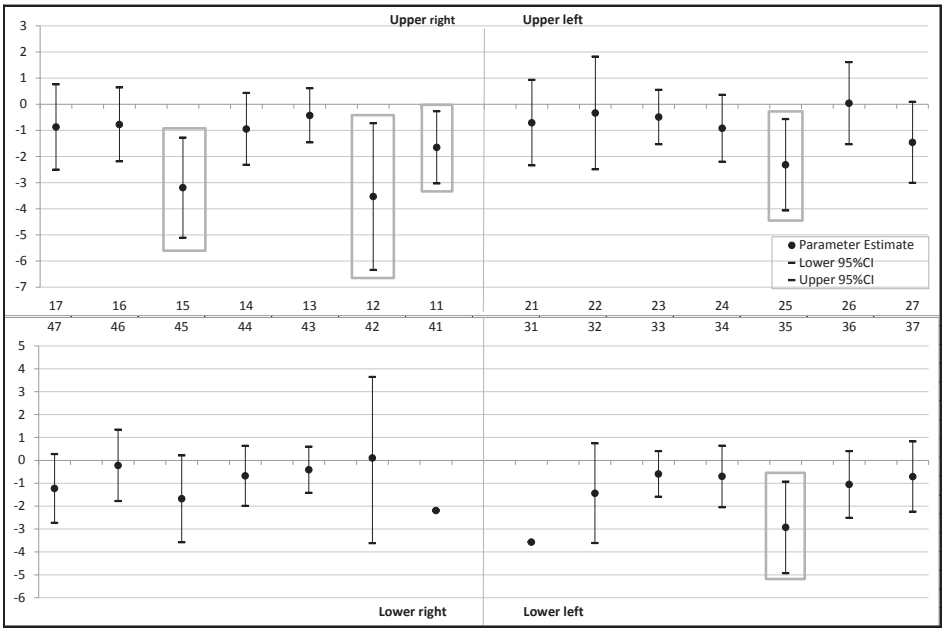
As shown in Figure 4.2.1, the ordinal regression analysis revealed a statistically significant association of oligodontia as part of ED with the delayed developmental stages of the right central incisor (PE, -1.65; 95% CI: -3.03, -0.27), the right lateral incisor (PE, -3.53; 95% CI: -6.34, -0.73), the right second premolar (PE, -3.19; 95% CI: -5.11, -1.28) and the left second premolar (PE, -2.32; 95% CI: -4.07, -0.57).

2- Mandibular teeth

The ordinal regression analysis, as presented in Figure 4.2.1, showed a statistically significant association of oligodontia as part of ED with the developmental stages of the left second premolar (PE, -2.93; 95% CI: -4.93, -0.93).

3- Antagonists of agenetic teeth

Figure 4.2.1. The association between oligodontia-ED and stage of development for each present tooth



Abbreviations: The ordinal regression model was fully adjusted for age, sex, number of missing teeth and number of filled teeth; the statistically significant parameter estimates are presented inside the grey squares

The results of the studied association between agenesis of a certain tooth and development of the correspondent in the other jaw are shown in supplementary Figure S4.2.1.

The abnormal shape of teeth

As shown in Table 4.2.4, oligodontia as part of ED was associated with the abnormal shape of teeth (OR, 8.51; 95% CI: 3.14, 23.03) in Model 1. The association of non-isolated oligodontia with the abnormal shape of teeth remained still statistically significant ($p<0.001$) in Model 2, however the effect estimate decreased (OR 6.54; 95% CI: 2.34, 18.28).

The abnormal size of teeth

The effect estimates obtained in Model 1 and Model 2 of the logistic regression analysis did not present distinctive differences between isolated oligodontia and oligodontia-ED (Table 4.2.4). Considering all the possible confounders in Model 2, oligodontia as part of ED (OR, 2.16; 95% CI: 0.67, 7.00) was not statistically significantly associated with the abnormal size of teeth.

Table 4.2.4. The associations of oligodontia-ED with abnormal shape and abnormal size of teeth

	Model 1			Model 2		
	OR	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
Abnormal shape (isolated oligodontia; ref.)	8.51	3.14, 23.03	*<0.001*	6.54	2.34, 18.28	*<0.001*
Abnormal size (isolated oligodontia; ref.)	1.19	0.79, 6.20	0.132	2.22	0.73, 6.75	0.160

Abbreviations: OR –odds ratios, CI – confidence interval, ref.-reference; significant p-values are presented in italic font
Model 1: the association between non-isolated oligodontia and abnormal shape is adjusted for age and sex
Model 2: was additionally adjusted for number of missing teeth and number of filled teeth

4.2.4 DISCUSSION

In this study, we investigated the phenotypic differences in dental development between patients with isolated oligodontia and non-isolated oligodontia, as part of ectodermal dysplasia. Patients with oligodontia-ED showed disturbances in dental development the most. The disturbed development of teeth in oligodontia-ED was mainly expressed in the higher frequency of missing the central incisors and second molars in both jaws, and the lower lateral incisors. Furthermore, a delayed maturation of the permanent dentition of approximately 10 months to one year and a half was shown when compared with isolated oligodontia patients. Specifically, the development of the maxillary teeth, such as right central incisor, right lateral incisor, right second premolar and left second premolar were around 2-4 stages delayed. As regarding to the mandibular teeth, the left second was approximately 3 stages delayed in development when being present. Abnormal shape of teeth was approximately seven times more evident in patients with oligodontia-ED than in patients with isolated oligodontia.

Our findings were consistent with the literature, since patients with oligodontia-ED are expected to show more disturbances in dental development than patients with isolated oligodontia due to the higher occurrence of dental anomalies affecting the number, size and shape of teeth [10,33]. The non-isolated trait of oligodontia is characterized by more agenetic teeth than isolated oligodontia [10,34], shown in our study as well. The lower second premolars and upper lateral incisors are recognized as the most frequent congenitally missing teeth [3, 35]. Consistently, second premolars and lateral incisors were among the most prevalent missing teeth in both groups of isolated oligodontia and oligodontia-ED. Beside the common agenetic teeth, the frequency of missing the central incisor and second molar was distinctive for ED patients. While absence of the central incisor indicates dental agenesis of 9 or more teeth, the absence of the second molar is to our best knowledge not previously mentioned to distinguish patients with oligodontia-ED [23]; raising the question whether the agenetic second molar could be a potential phenotypic indicator of ED. Even though the teeth noted as the most prevalent missing showed statistically significantly delayed developmental stages when present, the delay in maturation of all permanent teeth was a general trend in patients with oligodontia-ED. We obtained more significant differences for the development of maxillary teeth than for the development of mandibular teeth. Considering the trend

of mandibular teeth being more frequently agenetic than maxillary teeth, a distinguished delay of development in mandibular teeth was expected [35]. However, the antagonists of the most common missing teeth in patients with oligodontia tended to present lower stages of development, linking the agenesis of a certain tooth with the delayed development of the antagonist (supplementary Figure S4.2.1).

As expected, patients with ED had a significant higher frequency of malformed teeth mainly expressed for maxillary canines and central incisors. The conical shape of the crown in canines and notched marginal edge in incisors were notable in 64% of oligodontia-ED patients. The shape of dental crown is determined by the shape of the enamel layer deposited upon the dentin layer [36,37]. As the only dental tissue originating from ectoderm, enamel is the main bridge that links disturbances in maturation of teeth with ectodermal dysplasia. Abnormal formation and mineralization of enamel can influence the shape of dental crown and the developmental stages of the affected teeth as a matter of calcification process [38]. Hence, more malformed teeth and delayed stages of calcification can distinguish patients with oligodontia as part of ED from patients with isolated oligodontia, explaining our findings. Smaller tooth size characterizes patients with isolated and non-isolated oligodontia [26,35,39]. As a comparison of the two conditions in our study, the abnormal size of teeth was not a distinctive characteristic for oligodontia-ED compared with isolated oligodontia.

Clinical reports describe isolated oligodontia as a condition that can be associated with appearance of abnormal ectodermal features from hair, nails or sweat glands [23]. Hence, the distinction of isolated oligodontia from non-isolated oligodontia becomes a common clinical concern in patients with ectodermal dysplasia. Recently, genetic mutations of *EDARADD* implicated in the condition of ED, are shown to be associated with isolated oligodontia, as well [23]. Thus, a proper differentiation between the both conditions is a necessity. The combination of genotyping and phenotyping characteristics in patients with isolated oligodontia-ED would be the best solution to achieve the distinction of one condition from the other in a clinical and literary perspective. The lack of genetic confirmation in isolated oligodontia limited us to attach information on genetic variants to each patient. Furthermore, we could not obtain additional information about the abnormal ectodermal symptoms affecting salivary secretion, hair, skin or nails if present in isolated and non-isolated oligodontia. However, in order to help the distinction of isolated oligodontia from non-isolated oligodontia especially when: a genetic test is not performed and the abnormal features of ectoderm are not evident in the clinical examination, we assessed the dental development phenotype for each patient and additionally defined the specific dental differences between the both conditions.

In the current study, the measurements on dental development are based on DPRs. A DPR is an important diagnostic tool in the dental clinical practice, though detailed information on abnormal size and abnormal shape of teeth can be missed during the investigation of DPRs. Hence, we used the intraoral pictures additionally to extract the most accurate information.

Although oligodontia is a rare congenital anomaly, it carries on an esthetical, functional, psychological and financial burden for all the patients [40,41]. This study includes only ectodermal dysplasia, as the most common syndromic condition where oligodontia is manifested as a non-isolated trait which leaves in shadow many other rare syndromes. However, non-

isolated oligodontia is reported as a seldom congenital anomaly, limiting the performance of studies in this group of patients.

Our findings suggest that oligodontia-ED can be distinguished from isolated oligodontia by more agenetic second molars, evident abnormal shape of incisors and canines, and an approximate one year delayed development of the present teeth, reflected in the developmental stages of maxillary premolars the most. In conclusion, phenotypic differences in dental development exist between isolated oligodontia and oligodontia-ED and should be recognized to facilitate the differential diagnosis between the both conditions.

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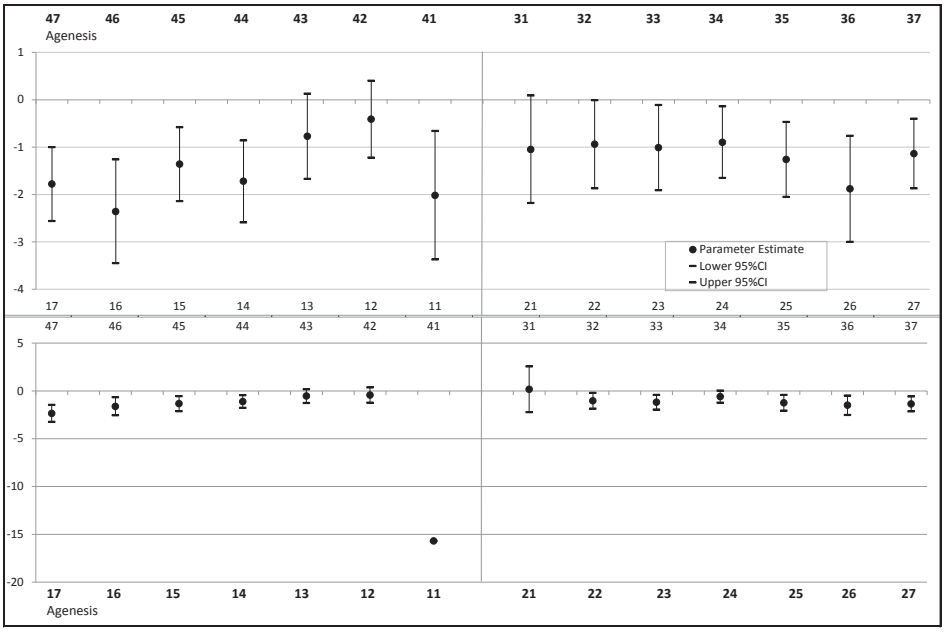
SUPPLEMENT

Table S4.2.1

Developmental stages (0-8) of teeth				Distribution of missing teeth		
FDI Code	**Isolated oligodontia** (N = 129)	**Oligodontia-ED** (N = 22)	**p-value**	**Isolated oligodontia** (N = 129)	**Oligodontia-ED** (N = 22)	**p-value**
11	8 (7-8)	8 (0-8)	*0.001*	4 (3.1)	5 (22.7)	*0.004*
12	0 (0-8)	0 (0-8)	0.632	85 (65.9)	14 (63.6)	0.507
13	6 (0-8)	6 (0-8)	0.912	36 (27.9)	5 (22.7)	0.414
14	0 (0-7)	0 (0-6.3)	0.557	71 (55.0)	13 (59.1)	0.454
15	0 (0-6)	0 (0-5.1)	0.913	93 (72.1)	15 (68.2)	0.442
16	8 (0-8)	8 (0-8)	0.169	19 (14.7)	3 (13.6)	0.597
17	5 (0-7)	0 (0-7.1)	*0.011*	43 (33.3)	16 (72.7)	*0.001*
21	8 (7-8)	8 (0-8)	*0.028*	5 (3.9)	5 (22.7)	*0.006*
22	0 (0-8)	0 (0-8)	0.460	83 (64.3)	16 (72.7)	0.306
23	6 (0-8)	6 (0-8)	0.577	31 (24.0)	6 (27.3)	0.464
24	0 (0-8)	1.5 (0-7.1)	0.817	71 (55.0)	11 (50.0)	0.416
25	0 (0-6)	0 (0-5.1)	0.829	89 (69.0)	15 (68.2)	0.560
26	8 (0-8)	8 (0-8)	0.307	16 (12.4)	3 (13.6)	0.549
27	5 (0-7)	0 (0-7)	*0.005*	46 (35.7)	15 (68.2)	*0.004*
31	7 (0-8)	0 (0-8)	*0.004*	62 (48.1)	18 (81.2)	*0.003*
32	8 (0-8)	0 (0-8)	*0.003*	39 (30.2)	14 (63.6)	*0.003*
33	7 (0-8)	7 (0-8)	0.805	20 (15.5)	4 (18.2)	0.478
34	5 (0-8)	0 (0-7.1)	0.161	49 (38.0)	12 (54.5)	0.110
35	0 (0-5)	0 (0-5.1)	0.471	101 (78.3)	15 (68.2)	0.218
36	8 (7-8)	7.5 (0-8)	*0.012*	14 (10.9)	5 (22.7)	0.117
37	4 (0-7)	0 (0-7)	*0.023*	55 (42.6)	15 (68.2)	*0.023*
41	0 (0-8)	0 (0-8)	*0.009*	66 (51.2)	18 (81.8)	*0.006*
42	8 (0-8)	0 (0-8)	*0.008*	48 (37.2)	15 (68.2)	*0.007*
43	7 (0-8)	7 (0-8)	0.650	21 (16.3)	3 (13.6)	0.522
44	5 (0-8)	0 (0-8)	0.131	47 (36.4)	12 (54.5)	0.086
45	0 (0-6)	0 (0-5.1)	0.937	96 (74.4)	16 (72.7)	0.526
46	8 (6.3-8)	8 (0-8)	0.208	15 (11.6)	4 (18.2)	0.290
47	4 (0-7)	0 (0-7)	*0.017*	53 (41.1)	15 (68.2)	*0.017*

Abbreviations: Differences in missing each tooth between oligodontia-ED and isolated oligodontia are presented in p-values obtained from chi-squared test, significant p-values are presented in italic font

Figure S4.2.1. The association of the agenesis of a certain tooth with the development of the antagonist



Abbreviations: The ordinal regression model was fully adjusted for age, sex, number of missing teeth and number of filled teeth; The statistically significant associations do not cross the reference axis (zero)