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Tooth Agenesis Association with Self-reported Family History of Cancer

ABSTRACT

It has been proposed that tooth agenesis and cancer development share common molecular pathways. We performed a cross-sectional study to investigate the epidemiological and molecular association between tooth agenesis and self-reported family history of cancer. Eighty-two individuals with tooth agenesis and 328 individuals with no birth defect were recruited from the same institution. Tooth agenesis was assessed in permanent teeth and was defined based on the age of the participants and when initial tooth formation should be radiographically visible. We also investigated the role of genes involved in dental development that have been implicated in tumorigenesis, and 14 markers in *AXIN2, FGF3, FGF10*, and *FGFR2* were genotyped. Individuals with tooth agenesis had an increased risk of having a family history of cancer (p = 0.00006; OR = 2.7; 95% C.I., 1.6-4.4). There were associations between *AXIN2, FGF3, FGF10*, and *FGFR2* with tooth agenesis [*i.e.*, individuals who carried the polymorphic allele of *FGFR2* (rs1219648) presented higher risk for having premolar agenesis (p = 0.02; OR = 1.8; 95% C.I., 1.1-3.0)]. In conclusion, tooth agenesis was associated with positive self-reported family history of cancer and with variants in *AXIN2, FGF3, FGF10*, and *FGFR2*. Prospective studies are needed to confirm if tooth agenesis can be used as a risk marker for cancer.

KEY WORDS: stomatognathic diseases, tooth diseases, tooth abnormalities, anodontia, neoplasms, neoplastic processes.

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INTRODUCTION

Evidence for common pathways in congenital craniofacial anomalies and cancer development comes from studies that show the occurrence of both conditions in the same individuals or higher frequency of cancer in families of individuals born with cleft lip and palate (Mili *et al.*, 1993; Zhu *et al.*, 2002; Lammi *et al.*, 2004; Bille *et al.*, 2005; Bjørge *et al.*, 2008; Menezes *et al.*, 2009; Taioli *et al.*, 2010; Jindal and Vieira, 2012; Vieira *et al.*, 2012; Yildirim *et al.*, 2012). Cancer is a heterogeneous pathology with clinical and etiological diversity. Self-reported medical history may not be precise, and inaccurate reporting of family history information may result in cancer misclassification. However, most population studies rely on self-reported family history of cancer. Self-reported family history is one of the factors most consistently associated with increased risk of developing cancer (Ziogas and Anton-Cluver, 2003; Murff *et al.*, 2004).

Tooth agenesis is the most common congenital craniofacial anomaly in humans. The prevalence of missing permanent teeth in the general population, excluding third molars, is around 4.8% (Küchler *et al.*, 2008), and this anomaly is more common in individuals born with oral clefts than in the general population, suggesting that both conditions share the same genetic background (Letra *et al.*, 2007).

Animal models have demonstrated that the genes which play an important role in cancer development are also involved in dental development. A transgenic mouse model of the nevoid basal cell carcinoma syndrome expressing Sonic hedgehog (*Shh*) in basal epithelium under a Keratin-14 promoter will have dental development arrested at the bud stage under conditions of high levels of *Shh* expression (Cobourne *et al.*, 2009).

Based on this evidence, we hypothesized that individuals with tooth agenesis and their relatives would have a higher risk of cancer, and, consequently, that genes involved in tumorigenesis may also be involved in the etiology of tooth agenesis. Therefore, we aimed to investigate the self-reported occurrence of cancer among individuals and families with tooth agenesis and to evaluate the association between *AXIN2, FGF3, FGF10*, and *FGFR2* with this congenital anomaly.

Participants & Methods

The Human Ethics Committee of the Health Department of the city of Rio de Janeiro, Brazil (113/09) and the University of Pittsburgh Institutional Review

Table 1. *AXIN2, FGF3, FGF10,* and *FGFR2* Markers Studied

Gene	Variants	Locus	Base Change	Average Heterozygosity ± Standard Error	Minor Allele Frequency
AXIN2	rs2240308	17q23-q24	A/G	0.417 ± 0.186	0.324
	rs740026[a]		A/G	0.402 ± 0.198	0.291
FGF3	rs12574452	11q13.3	A/G	0.444 ± 0.157	0.328
	rs1893047		A/G	0.492 ± 0.062	0.428
	rs4631909		C/T	0.498 ± 0.031	0.479
	rs7932320		A/G	0.458 ± 0.139	0.486
	rs4980700		A/G	0.492 ± 0.061	0.440
FGF10	rs1448037	5p12	C/T	0.426 ± 0.178	0.361
	rs1011814		C/T	0.489 ± 0.072	0.485
	rs11750845		C/T	0.458 ± 0.139	0.379
	rs900379		C/T	0.495 ± 0.048	0.482
	rs1448037		A/G	0.428 ± 0.175	0.361
	rs593307		C/T	0.430 ± 0.173	0.364
FGFR2	rs1219648	10q26	A/G	0.481 ± 0.095	0.402

Obtained from the following databases: http://www.ncbi.nlm.nih.gov, http://genome.ucsc.edu.
[a]The marker is a coding change in the gene (P50S: proline to serine at position 50).

Board approved this study. Informed consent was obtained from all participating individuals or parents/legal guardians.

We performed a cross-sectional single-center study. All participants were recruited from the same institution, the Federal University of Rio de Janeiro, between July 2009 and July 2011, in an attempt to select cases and control individuals with similar ethnicity, age, and social-culture backgrounds. Although the prevalence of tooth agenesis is higher in females, we did not attempt to match the sex, because it is expected that there will be the same number of males and females within any given family (World dataBank, 2012).

Data on self-reported family history of cancer were collected *via* a structured questionnaire, and a dental examination was performed during each participant's dental visit at the Federal University of Rio de Janeiro. Data about family history of cancer in all first- and second-degree relatives of the index case were included. If at least one of the family members had cancer, that participant was considered to have a family history of cancer.

Eight individuals with previous tooth extraction were excluded from the sample, since it was not possible to exclude the possibility of tooth agenesis. Among those not affected by tooth agenesis, two with a self-reported family history of tooth agenesis were excluded from the sample. No participants were found to have oral clefts or an underlying syndrome. Tooth agenesis was assessed in permanent teeth by visual and radiographic examinations. It was defined based on the age of the participants and when initial tooth formation should be visible in the radiographs (second premolar agenesis was considered only in individuals older than 8 yrs of age). Missing third molars were not considered in this study (Küchler *et al*., 2008).

DNA Samples and Genotyping

Genomic DNA for molecular analysis was extracted from buccal cells. *FGF3, FGF10*, and *FGFR2* were selected based on our previous observations that these genes are associated with specific types of cleft lip and palate with tooth agenesis (Menezes *et al*., 2008). *AXIN2* was chosen because we found it associated with families with segregating cleft lip and palate and with cancer reported more often (Menezes *et al*., 2009). Fourteen markers in the 4 genes (Table 1) were genotyped by polymerase chain-reactions with the Taqman method performed with the Stratagene Mx3005P real-time PCR system (Stratagene, La Jolla, CA, USA) and a ABI PRISM® 7900HT Sequence Detection System (Foster City, CA, USA). Pre-designed probes were supplied by Applied Biosystems (Foster City, CA, USA). Markers were chosen based on allele frequency, position on the gene, and linkage disequilibrium relationships to maximize information content.

Statistical Analysis

Data were subsequently processed and analyzed with the Epi Info 3.3.2 statistical software package (http://www.cdc.gov/epiinfo). Results were reported according to the STROBE guidelines for observational studies. To gain statistical power, we had a ratio of 4:1 of control individuals to cases. Four hundred and ten persons were included (82 individuals with tooth agenesis and 328 unaffected persons). Student's *t* test at a significance level of 0.05 was used to assess the differences in means between individuals with and those without tooth agenesis. In addition, cases were analyzed not only as a total group, but also in stratified groups, such as types of cancer reported in the family and types of missing teeth. Odds ratio calculations and chi-square or Fisher's exact tests at a significance level of 0.05 were used to determine if any tooth agenesis subtypes were preferentially associated with any type of cancer, and if any tooth agenesis subtype was preferentially associated with any allele or genotype. Hardy-Weinberg equilibrium was evaluated by chi-square test with one degree of freedom within each marker.

Table 2. Demographic Data for the Study Participants

	Cases (n = 82)	Control Individuals (n = 328)	*p* value
Age, yrs (SD)	18.15 (10.2)	20.33 (14.9)	0.21**
Sex (%)			
Female	52 (63.4)	160 (48.8)	0.018*
Male	30 (36.6)	168 (51.2)	
Ethnic Background (%)			
Caucasian	56 (68.3)	202 (61.6)	0.26*
African descent	26 (31.7)	126 (38.4)	
Positive family history of oral clefts (%)	2 (2.43)	4 (1.21)	0.35*
Positive family history of cancer (%)	45 (54.9)	102 (31.1)	**0.00006***
Mean number of types of cancer reported in the same family (SD)	1.43 (0.67)	1.28 (0.76)	0.27*
Cancer in the Index Case (%)	–	1 (100)	0.13*
Cancer in the first-degree relatives of the Index Case (%)	6 (7.3)	28 (8.5)	
Cancer in the second-degree relatives of the Index Case (%)	39 (47.6)	73 (22.2)	
Characteristics of Cases	n	%	
Types of missing teeth			
Premolar agenesis	37	40.3	
Upper lateral incisor agenesis	34	36.9	
Lower incisor agenesis	13	14.1	
Canine agenesis	2	2.2	
Molar agenesis	6	6.5	
Affected Arch			
Maxilla	39	47.6	
Mandible	32	39.0	
Both	11	13.4	
Affected Side			
Left	16	19.5	
Right	27	32.9	
Positive family history of tooth agenesis	8	9.7	
Associated dental anomalies			
Yes	12	14.6	
No	70	85.4	

*Chi-square test.
**t test; Bold face indicates statistical significance. The total number of missing teeth was 147. Associated dental anomalies were: 5 conoid microdontia, 3 supernumerary teeth, 3 fused teeth.

RESULTS

Of the 82 individuals with tooth agenesis, eight reported family history of congenital missing teeth. Table 2 summarizes the studied population. There were no statistically significant differences in age and ethnicity between individuals with and those without tooth agenesis ($p > 0.05$). Individuals with tooth agenesis presented an increased risk for having a family history of cancer ($p = 0.00006$; odds ratio = 2.7; 95% confidence interval, 1.6-4.4). Eight individuals reported positive tooth agenesis history in their family members, but they did not report a family history of cancer. There was no difference in the distribution of the sexes of the index cases by positive family history of cancer ($p = 0.82$).

Among the participants with tooth agenesis, four had oligodontia (tooth agenesis of 6 or more teeth), one had 4 congenitally missing teeth, five had 3 missing teeth, 29 had 2 missing teeth, and the remaining 43 individuals had just 1 missing tooth.

Breast cancer was the most common cancer reported, followed by prostate cancer, in both those with and those without tooth agenesis. Table 3 shows the distribution of the types of cancer in the studied population. Individuals with tooth agenesis had an increased risk of having a family history of female cancers: breast, ovarian, and cervical uterine cancer ($p = 0.0013$; odds ratio = 2.9; 95% confidence interval, 1.5-5.8). We also observed an increased frequency of family history of breast cancer ($p = 0.0005$; odds ratio = 4.9; 95% confidence interval, 1.6-14.0) and prostate cancer ($p = 0.0043$; odds ratio = 5.6; 95% confidence interval, 1.7-17.8) in individuals with at least 1 missing premolar. In the group with at least 1 missing upper lateral incisor, an increased frequency of all cancers ($p = 0.0011$; odds ratio = 3.17; 95% confidence interval, 1.4-6.8) was found.

All genotypes were in Hardy-Weinberg equilibrium. Table 4 provides a summary of the results in the markers studied. Some markers were associated with tooth agenesis as well as its subtypes. *AXIN2* rs2240308 was associated with cases with lower

Table 3. Types of Cancer Distribution in Cases and Control Individuals

Type of Cancer	Cases (%)	Control Individuals (%)	*p* value	Odds Ratio (95% Confidence Interval)
Bladder	1 (1.2)	4 (1.2)	1.000	1.0 (0.11-9.0)
Brain and nervous system	3 (3.7)	1 (0.3)	**0.026**	12.4 (1.2-120.9)
Bone	1 (1.2)	1 (0.3)	0.360	4.0 (0.2-65.2)
Breast	10 (12.2)	15 (4.6)	**0.009**	2.9 (1.2-6.7)
Cervical uterus	5 (6.1)	11 (3.4)	0.251	1.8 (0.6-5.5)
Esophagus	1 (1.2)	1 (0.3)	0.360	4.0 (0.24-65.2)
Head and neck	–	2 (0.6)	0.639	–
Intestine and colon	5 (6.1)	7 (2.1)	0.093	2.9 (0.9-9.6)
Lymphoma	3 (3.7)	4 (1.2)	0.146	3.0 (0.6-14.0)
Liver	–	7 (2.1)	0.207	–
Lung	6 (7.3)	10 (3.0)	0.074	2.5 (0.8-7.1)
Ovary	1 (1.2)	1 (0.3)	0.360	4.0 (0.2-65.2)
Pancreas	1 (1.2)	2 (0.6)	0.488	2.0 (0.2-22.4)
Prostate	9 (11.0)	11 (3.4)	**0.004**	3.5 (1.4-8.8)
Kidney	1 (1.2)	2 (0.6)	0.488	2.0 (0.2-22.4)
Skin	3 (3.7)	7 (2.1)	0.425	1.7 (0.4-6.8)
Stomach	2 (2.4)	13 (4.0)	0.394	0.6 (0.13-2.7)
Throat	1 (1.2)	3 (0.9)	0.591	1.3 (0.13-13.0)
Other cancers	1 (1.2)	4 (1.2)	–	–
Unknown cancer[#]	5 (6.1)	10 (3.0)	–	–

[#]Includes 1 of each of the following: abdominal, leukemia, larynx, thyroid, and pleura.

incisor agenesis ($p = 0.04$; odds ratio = 2.22; 95% confidence interval, 1.0-4.9). Upper lateral incisor agenesis was associated with *FGF3* rs12574452 ($p = 0.003$), and lower lateral incisor agenesis was associated with *FGF3* rs7932320 ($p = 0.042$). Finally, *FGF10* rs11750845 genotype distribution was statistically different in all cases of tooth agenesis ($p = 0.043$), as well as in cases with upper lateral incisor agenesis ($p = 0.05$).

The *FGFR2* polymorphism rs1219648 was more common in cases with premolar agenesis than in control individuals ($p = 0.02$; odds ratio = 1.8; 95% confidence interval, 1.1-3.0). Under the dominant model, the GG genotype increased the risk for premolar agenesis ($p = 0.0472$; odds ratio = 2.2; 95% confidence interval, 1.0-5.0).

DISCUSSION

We observed a higher frequency of almost all tumor types in families of individuals with tooth agenesis. The highest risk was observed mainly with brain/nervous system, prostate, and breast cancers. Borderline results were observed for lung and intestine/colon cancers. In contrast, in head and neck, liver, and stomach cancers, the trend appeared to be the opposite. However, *p* values were higher than 0.05, and the confidence interval demonstrated that tooth agenesis is probably not a protective factor for these cancer types. Even though head and neck cancer and tooth agenesis affect craniofacial structures, we did not find an increased risk of this kind of cancer in the relatives of those with tooth agenesis. This may suggest that these conditions do not share the same genetic contributors. In addition, we do not have information regarding smoking and drinking habits of the relatives. Alcohol consumption and smoking are known risk factors for oral cancer (and other types of the disease) and can potentially modify individual risks to this disease. If families of the studied individuals have little exposure to smoking and drinking, risks to oral cancer may be decreased in our study.

A previous study reported that women with epithelial ovarian cancer were 8.1 times more likely to have tooth agenesis than women without this condition (Chalothorn *et al.*, 2008). Ovarian cancer was an uncommon finding in our study, and only two individuals reported this condition. However, cancer types that typically occur in females were increased three-fold in families of persons with tooth agenesis in our data.

AXIN2 is involved in cell growth, proliferation, and differentiation. In our work, we found an association between individuals with lower incisor agenesis and *AXIN2* (rs2240308). A report of a four-generation Finnish family with its members segregating oligodontia and colon cancer or pre-cancerous polyps showed that these conditions were caused by mutations in *AXIN2* (Lammi *et al.*, 2004). In our study, we observed a borderline association between tooth agenesis and colon cancer. In the Finnish family with a mutation in *AXIN2* (Lammi *et al.*, 2004), the members presented a remarkable characteristic: Eleven out of 12 family members were found with lower incisor agenesis. In addition, our previous work also showed that variation in *AXIN2* is associated with oral clefts with tooth agenesis (Letra *et al.*, 2007) and with oral clefts in families that report a family history of cancer more often (Menezes *et al.*, 2009).

The fibroblast growth factor (FGF) family represents a group of heparin-binding, multifunctional polypeptides with mitogenic activity, involved in diverse processes including embryonic development, wound healing, tissue regeneration, and angiogenesis, as well as in autonomous tumor growth and tumor

Table 4. Genotype and Allele Distribution Summary Results

			Allele (%)†			Genotype (%)†			
Gene	rs#	Type of Tooth Agenesis	d	D	*p* value§	dd	dD	DD	*p* value§
AXIN2	rs2240308	Control	247 (38.0)	403 (62.0)	–	56 (17.3)	135 (41.5)	134 (41.2)	–
		All-tooth agenesis	62 (37.8)	102 (62.2)	0.961	13 (15.9)	36 (43.9)	33 (40.2)	0.922
		Premolar agenesis	24 (32.4)	50 (67.6)	0.358	5 (13.6)	14 (37.8)	18 (48.6)	0.826
		Upper lateral incisor agenesis	27 (39.7)	41 (60.3)	0.786	5 (14.7)	17 (50.0)	12 (35.3)	0.825
		Lower incisor agenesis	15 (57.7)	11 (42.3)	0.04*	4 (30.8)	7 (53.8)	2 (15.4)	0.157
	rs740026	Control	207 (31.7)	447 (68.3)	–	35 (10.7)	137 (41.9)	155 (47.4)	–
		All-tooth agenesis	53 (32.7)	109 (67.3)	0.792	8 (9.9)	37 (45.7)	36 (4.4)	0.836
		Premolar agenesis	23 (31.9)	49 (68.1)	0.963	5 (13.5)	14 (37.8)	18 (48.7)	0.723
		Upper lateral incisor agenesis	22 (32.4)	46 (67.4)	0.917	2 (5.9)	18 (52.9)	14 (41.2)	0.405
		Lower incisor agenesis	11 (42.3)	15 (57.7)	0.255	2 (15.4)	7 (53.8)	4 (30.8)	0.497
FGF3	rs12574452	Control	189 (31)	409 (69)	–	30 (10.0)	129 (43.1)	140 (46.8)	–
		All-tooth agenesis	46 (49.5)	98 (50,5)	0.937	5 (6.9)	36 (50.0)	31 (43.1)	0.501
		Premolar agenesis	18 (26.5)	50 (73.5)	0.385	3 (8.8)	12 (35.3)	19 (55.9)	0.602
		Upper lateral incisor agenesis	24 (41.4)	34 (58.6)	0.129	1 (3.4)	22 (75.9)	6 (20.7)	0.003*
		Lower incisor agenesis	7 (41.2)	10 (58.8)	0.403	1 (9.1)	5 (45.5)	5 (45.5)	0.986
	rs1893047	Control	298 (48.9)	312 (51.1)	–	77 (25.2)	144 (47.2)	84 (27.5)	–
		All-tooth Agenesis	72 (47.4)	80 (52.6)	0.743	16 (21.1)	40 (52.6)	20 (26.3)	0.157
		Premolar agenesis	29 (40.3)	43 (59.7)	0.168	5 (13.9)	19 (52.8)	12 (33.3)	0.313
		Upper lateral incisor agenesis	32 (53.3)	28 (46.7)	0.591	8 (26.7)	16 (53.3)	6 (20.0)	0.665
		Lower incisor agenesis	12 (50.0)	12 (50.0)	0.912	3 (25.0)	6 (50.0)	3 (25.0)	0.977
	rs4631909	Control	283 (45.9)	333 (54.1)	–	64 (20.8)	155 (50.3)	89 (28.9)	–
		All-tooth Agenesis	70 (46.0)	82 (54.0)	0.981	14 (18.4)	42 (55.3)	20 (26.3)	0.74
		Premolar agenesis	52 (38.8)	82 (61.2)	0.132	5 (14.3)	20 (57.1)	10 (28.5)	0.623
		Upper lateral incisor agenesis	30 (48.4)	32 (51.6)	0.712	6 (19.4)	18 (58.1)	7 (22.6)	0.685
		Lower incisor agenesis	10 (41.7)	14 (58.3)	0.680	2 (16.7)	6 (50.0)	4 (33.3)	0.917
	rs7932320	Control	269 (43.4)	351 (56.6)	–	60 (19.4)	149 (48.1)	101 (32.6)	–
		All-tooth agenesis	73 (45.6)	87 (54.4)	0.611	13 (16.3)	47 (58.8)	20 (25.0)	0.228
		Premolar agenesis	30 (40.5)	44 (59.5)	0.64	5 (13.5)	20 (54.1)	12 (32.40	0.655
		Upper lateral incisor agenesis	11 (42.3)	15 (57.7)	0.913	2 (15.4)	7 (53.8)	4 (30.8)	0.904
		Lower incisor agenesis	34 (53.1)	30 (46.9)	0.135	6 (18.8)	22 (68.8)	4 (12.5)	0.042*
	rs4980700	Control	287 (47.7)	315 (52.3)	–	70 (23.3)	147 (48.8)	84 (27.9)	–
		All-tooth agenesis	68 (45.3)	82 (54.7)	0.607	14 (18.7)	40 (53.3)	21 (28)	0.666
		Premolar agenesis	31 (47)	35 (53)	0.913	6 (18.2)	19 (57.6)	8 (24.2)	0.625
		Upper lateral incisor agenesis	12 (50.0)	12 (50.0)	0.823	4 (33.3)	4 (33.3)	4 (33.3)	0.551
		Lower incisor agenesis	27 (40.9)	39 (59.1)	0.295	4 (12.1)	19 (57.6)	10 (30.3)	0.335
FGF10	rs1448037	Control	396 (63.2)	230 (36.8)	–	131 (41.9)	134 (42.8)	48 (15.3)	–
		All-tooth agenesis	87 (58.0)	63 (42.0)	0.232	26 (34.7)	35 (46.7)	14 (18.7)	0.496
		Premolar agenesis	39 (55.7)	31 (44.3)	0.216	12 (34.3)	15 (42.9)	8 (22.9)	0.461
		Upper lateral incisor agenesis	36 (58.0)	26 (42.0)	0.419	10 (32.3)	16 (51.6)	5 (16.1)	0.563
		Lower incisor agenesis	12 (54.5)	10 (45.5)	0.405	3 (27.3)	6 (54.5)	2 (18.2)	0.624
	rs1011814	Control	368 (60.3)	242 (39.7)	–	119 (39.0)	130 (42.6)	56 (18.4)	–
		All-tooth agenesis	80 (55.5)	64 (44.4)	0.244	23 (31.9)	34 (47.2)	15 (20.8)	0.536
		Premolar agenesis	37 (52.8)	33 (47.2)	0.227	11 (31.4)	15 (42.9)	9 (25.7)	0.506
		Upper lateral incisor agenesis	32 (55.2)	26 (44.8)	0.443	8 (27.6)	16 (55.2)	5 (17.2)	0.39
		Lower incisor agenesis	11 (55.0)	9 (45.0)	0.632	3 (30.0)	5 (50.0)	2 (20.0)	0.843

(continued)

Table 4. (continued)

Gene	rs#	Type of Tooth Agenesis	Allele (%)†			Genotype (%)†			
			d	D	*p* value§	dd	dD	DD	*p* value§
	rs900379	Control	299 (47.8)	327 (52.2)	–	75 (24.0)	149 (47.6)	89 (28.4)	–
		All-tooth agenesis	75 (47.5)	83 (52.5)	0.947	16 (20.3)	43 (54.4)	20 (25.3)	0.55
		Premolar agenesis	34 (47.2)	38 (52.8)	0.93	7 (19.4)	20 (55.6)	9 (25.0)	0.657
		Upper lateral incisor agenesis	27 (42.2)	37 (57.8)	0.394	5 (15.6)	17 (53.1)	10 (31.3)	0.567
		Lower incisor agenesis	13 (54.2)	11 (45.8)	0.537	3 (25.0)	7 (58.3)	2 (16.7)	0.652
	rs11750845	Control	405 (67.5)	195 (32.5)	–	143 (47.7)	119 (39.7)	38 (12.7)	–
		All-tooth agenesis	90 (60.0)	60 (40.0)	0.082	33 (44.0)	24 (32.0)	18 (24.0)	0.043*
		Premolar agenesis	41 (60.3)	27 (39.7)	0.231	15 (44.1)	11 (32.4)	8 (23.5)	0.21
		Upper lateral incisor agenesis	37 (57.8)	27 (42.2)	0.118	14 (43.8)	9 (28.1)	9 (28.1)	0.05*
		Lower incisor agenesis	15 (68.2)	7 (31.8)	0.946	5 (45.5)	5 (45.5)	1 (9.1)	0.901
	rs1448037	Control	230 (36.7)	396 (63.3)	–	48 (15.3)	134 (42.8)	131 (41.9)	–
		All-tooth agenesis	63 (42.3)	86 (57.7)	0.21	14 (18.7)	35 (46.7)	26 (34.7)	0.496
		Premolar agenesis	26 (41.9)	36 (58.1)	0.419	5 (16.1)	16 (51.6)	10 (32.3)	0.563
		Upper lateral incisor agenesis	31 (44.3)	39 (55.7)	0.216	8 (22.9)	15 (42.9)	12 (34.3)	0.461
		Lower incisor agenesis	10 (45.5)	12 (54.5)	0.426	2 (18.2)	6 (54.5)	3 (27.3)	0.62
	rs593307	Control	201 (38.1)	327 (61.9)	–	41 (15.5)	119 (45.1)	104 (39.4)	–
		All-tooth agenesis	53 (44.2)	67 (55.8)	0.216	13 (21.7)	27 (45.0)	20 (39.4)	0.455
		Premolar agenesis	28 (48.3)	30 (51.7)	0.13	7 (24.1)	14 (48.3)	8 (27.6)	0.333
		Upper lateral incisor agenesis	79 (89.8)	9 (10.2)	0.645	1 (12.5)	5 (62.5)	2 (25.0)	0.613
		Lower incisor agenesis	18 (39.1)	28 (60.9)	0.886	4 (17.4)	10 (43.5)	9 (39.1)	0.97
FGFR2	rs1219648	Control	238 (40.0)	360 (60.0)	–	49 (16.4)	140 (46.8)	110 (36.8)	–
		All-tooth agenesis	66 (42.9)	88 (57.1)	0.490	18 (23.4)	30 (39.0)	29 (37.7)	0.282
		Premolar agenesis	37 (54.4)	31 (45.6)	0.02*	11 (32.4)	15 (44.1)	8 (23.5)	0.052
		Upper lateral incisor agenesis	10 (38.5)	16 (61.5)	0.891	2 (15.4)	6 (46.2)	5 (38.5)	0.99
		Lower incisor agenesis	23 (35.9)	41 (64.1)	0.547	7 (21.9)	9 (28.1)	16 (50.0)	0.129

All tooth agenesis subgroups were compared with the control group.
†Upper-case letters denote the more frequent allele in controls.
§Chi-square test was used.
*Statistically significant results.

vascularization (Bikfalvi *et al*., 1997). Alterations in the gene expression of a number of FGF/FGFR family members have been reported in human breast cancer (reviewed by Wesche *et al.*, 2011), and analysis of genome-wide association data suggests that *FGFR2* contributes to breast cancer (Easton *et al.*, 2007). Mutations in *FGFR2* and *FGFR3* were also associated with colorectal cancer (Jang *et al.*, 2001). Studies in prostate cancer have also demonstrated that several *FGF*s and their receptors are up-regulated in this type of cancer (reviewed by Wesche *et al.*, 2011). Breast and prostate cancer were the most common types of cancer reported by the families included in our study sample.

Fgf signals play crucial roles in tooth initiation and further development in odontogenesis. Without the Fgf signal, the tooth does not develop beyond the bud stage (Porntaveetus *et al.*, 2011). Menezes *et al*. (2008) found an association for *FGF3* and *FGF10* with oral cleft subphenotypes. When tooth agenesis data were considered in the analysis, an increased risk for carrying variant alleles of *FGF10* and *FGFR2* could also be seen. In our sample, *FGF3* (rs12574452) and *FGF10 (*rs11750845) were associated with upper lateral incisor agenesis. In a subgroup with lower incisor agenesis, the *FGF3* rs7932320 genotype distribution was statistically different from that found in control individuals.

There are some important limitations to our study, and the results should be interpreted with caution. Family studies of cancer are often used as a marker of risk factors for this pathology. Accurate reports of cancer by relatives, combined with family history data, often form the basis for inferences about cancer risk factors and patterns of susceptibility, but individual self-reports may be inaccurate and biased. Our tooth agenesis group presented more females than the control group, and one can argue that females may be more aware of specific types of diseases running in their families (*i.e.*, breast cancer). Previous studies showed that the quality of self-reported cancer history varies according to the site of the cancer; however, the accuracy of patient reports of cancer among their family members is quite reliable for most cancer sites (Ziogas and Anton-Cluver, 2003; Murff *et al.*, 2004). There is evidence that women report cancer that typically occurs in females more accurately than do men (Murff *et al.*, 2004).

It is expected that a genetic link between cancer and tooth agenesis would manifest more strongly in first-degree relatives (Vieira *et al.*, 2012). In our study, cancer was twice as frequent in the second-degree relatives of individuals with agenesis as compared with that in control individuals, while in first-degree relatives the incidence was approximately the same in the two groups. However, this could be explained by the fact that our tooth agenesis cases are young, and their parents and siblings are also young and have yet to develop any kind of cancer.

Our findings highlight the potential association between tooth agenesis and cancer. The possibility of the identification of a dental clinical marker for cancer brings additional interest to the studies of the association between these 2 conditions, as well as to the genetic regulation of dental development. Familial studies, including families with many affected members, are needed and could add more insight into possible common molecular pathways.

Our study supports the hypothesis that both tooth agenesis and cancer share a similar genetic background. We found an increased overall cancer occurrence in families of individuals with tooth agenesis. Moreover, *AXIN2, FGF3, FGF10*, and *FGFR2* are associated with tooth agenesis.

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