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Genetic Etiology of Development Alterations Affecting the Number, Size, Form, Structure and Eruption of the Teeth

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Abstract

Teeth develop in the mammalian embryo via a series of interactions between the odontogenic epithelium and the neural crest-derived ectomesenchyme of the early jaw primordia. The molecular interactions required to generate a tooth are mediated by families of signaling molecules, which often act reiteratively in both a temporal and spatial manner. In humans, the process of odontogenesis lasts approximately 18 years, beginning in the 6th-8th week in the uterus and ending with the formation of the third molars in late adolescence. Each tooth passes through a series of stages that follow the same pattern, beginning with the formation of the bud, then cap and bell, followed by the deposit of enamel and dentin on the crown of the tooth. After the crown is formed, the development of the roots continues and finally the teeth emerge in the oral cavity, when about 2/3 of the roots have formed. Alterations in the indicated processes lead to a wide range of abnormalities that affect the number, size, shape of teeth and structural defects in mineralized tissues, as well as failures in dental eruption. The prevalence of these disorders may be as common as 2, 4% in hypodontia or extremely rare as 1 in 100,000 in dentin dysplasia. The spectrum of these anomalies, which may

occur in isolation or as part of syndromes is variable; being very mild to severe and very severe. Most of the knowledge about mammalian odontogenesis comes from studies in animal models, mainly mouse. However, the murine dentition is not equal to human dentition, so there are a series of aspects of tooth development in our species that remain unanswered. In this context, the clinical and molecular genetics study of families with various dentition disorders is a valuable approach that will contribute to improve our knowledge of the phenotype-genotype correlations involved in these abnormalities.

Keywords

Odontogenesis; Alterations; Tooth development

Introduction

Normal Odontogenesis

Dental formation and development in humans occurs from the 6th week in utero to adolescence [1]. In this process, reciprocal interactions between the epithelium and mesenchyme play a key role, mediated by seven signaling pathways: WNT, BMP, FGF, SHH, EDA, TNF and NOTCH which affect gene expression networks regulated by transcription factors (TF) [2,3]. The initiation stage begins with the appearance of the dental lamina in which the TF Pitx2, Foxi3, Dlx2, Lef1, p63 are expressed associated with the acquisition of tooth destination and odontogenic potential in the oral epithelium. The dental lamina also expresses signaling molecules such as Shh, Bmp2, Bmp4, Bmp7, Fgf8, Fgf9, Wnt10a and Wnt10b which function as mediators of odontogenic potential from the epithelium to the mesenchyme [2,3]. Morphogenesis of the tooth in mammals begins in structures called placodes in the incisor and molar regions. In the placodal cells, which form the early signaling centers, genes like Pitx2, Foxi3 and signaling molecules like Shh, Wnt10, Bmp2 and Fgf20 are expressed determining the proliferation and growth of the placodal epithelium, which gives rise to the bud. This stage is critical in determining the number and position of the teeth to be formed. At the tip of the dental bud the primary enamel knot is formed, where some cells leave the cell cycle due to the localized expression of p21, signaling molecules and genes linked to signaling pathways. These signals stimulate the growth of the flanking epithelium, which originates the cervical loop, moving the morphogenesis phase from bud to cap [2,3]. The enamel knot matures and in the bell stage epithelial growth and folding determine the shape and size of the crown. In molars the appearance of secondary enamel knots is induced, which express the same signals as the primary knot, but determine the size, positions, and heights of the cusps. During cytodifferentiation, in the bell stage, enamel and dentin are synthesized at the epithelial-mesenchymal interface, by the interaction of the same signals present in dental morphogenesis [2,3]. The development of the root begins after the formation of the crown. The apical region of the dental organ elongates and originates the Hertwig's epithelial root sheath (HERS), which grows apically guiding the formation of the root(s) and determining their number, size and shape. The inner layer of the sheath interacts with the mesenchyme, producing laminin-5 and growth factors that induce the differentiation of odontoblasts that secrete root dentin. The cells from HERS control the formation of cementum by the cells of the dental follicle [4]. Abnormalities in the indicated processes lead to a wide range of abnormalities that affect the number, size, shape of teeth and structural defects in mineralized tissues, as well as failures in dental eruption. Abnormal dental phenotypes are within a spectrum of severities: normal variation, isolated dental anomalies, cosegregation with non-dental defects or are part of a more severe syndrome. All current evidence suggests that

genetic, epigenetic and environmental factors contribute either individually or combined to produce this spectrum of anomalies [5,10].

Development Alterations Affecting the Number of Teeth

Selective Dental Agenesis

Selective tooth agenesis or congenital absence of teeth corresponds to the lack of development of teeth in the Primary Dentition (PrD) and/or Permanent Dentition (PeD) [9,11]. It is classified as: anodontia, which refers to an absolute lack of development of teeth; hypodontia, denoting lack of development of one or more teeth; and oligodontia, indicating lack of development of six or more teeth, excluding third molars [9,11]. The lack of teeth in PrD has a prevalence of less than 1% [9].The primary teeth most frequently absent are the maxillary lateral incisors and mandibular incisors. The prevalence of agenesis in permanent teeth ranges from 3% to 10%, without considering third molars. If the third molars are considered, the prevalence is 20% [9].The teeth most affected by agenesis are third molars, then molars, second premolars and lateral incisors. Ethnic and gender differences have been reported, with the Asian population being the most affected and the female sex [10,12]. A large percentage of cases of primary hypodontia are inherited in autosomal dominant form, with incomplete penetrance and variable expressivity, whereas a minority has autosomal recessive or sex-linked patterns [12,16].The environment plays an important role and in some cases, multifactorial inheritance has been suggested [6,8].Genes involved in isolated dental agenesis are shown in table 1 [12,16].The genes associated with syndromic hypodontia are approximately 43, some of which overlap with genes involved in isolated hypodontia[15]. Agenesis has been associated with various syndromes [5], lip and palate fissures [17], colon cancer [18], breast [18,19], ovarian cancer [20] and the presence of tumors in general [21], suggesting that agenesis may have a prospective predictive value for neoplasms [21]. In addition, a study evaluating the impact of moderate to severe hypodontia on the quality of life and self-esteem of those affected revealed that this condition has a negative effect on quality of life, but not on self-esteem [22].

Hyperdontia

It corresponds to the development of an increased number of teeth, called supernumerary teeth (ST). ST are teeth or tooth-like structures in addition to the 20 primary teeth and 32 permanent teeth [9,23,24]. They appear in any region of the dental arch, as single or multiple teeth, can be uni or bilateral and may be associated with some syndrome [9]. Hyperdontia correlates positively with macrodontia and it is more frequent in males than females (2:1) [9]. The exact etiology of hyperdontia is not clear. Three hypotheses have been postulated: phylogenetic reversion, dichotomy of the dental bud and hyperactivity of the dental lamina [9,25]. Clinical complications related to ST include failure of eruption, rotation or displacement, dilacerations, root resorption, crowding, malocclusion, formation of cysts and fistulas, eruption in the nasal cavity and delayed root development of permanent teeth [9,23-25].In PrD the prevalence of hyperdontia fluctuates between 0.2% and 0.8%. In permanent dentition (PeD) it ranges from 0.1% to 3% (Caucasians), in the general population it is 0.5% to 5.3% and in Asians the prevalence is slightly higher [9]. 76-86% of hyperdontia cases involve single teeth, 12% involve two extra teeth and less than 1% may involve three or more teeth [9].Single tooth hyperdontia occurs more frequently in PeD, in the maxilla and in the anterior region. Conical mesiodens are the most common ST and occur more frequently in the maxillary incisor region, followed by maxillary and molar quarters, premolars, canines, and mandibular incisors [9].Supernumerary mandibular incisors are very rare and most of the extra

teeth are unilateral. Multiple ST occurs more frequently in the mandible, in the premolar region followed by the molar and anterior regions [24]. An ST located in the anterior incisor region is called mesiodens, a fourth accessory molar is called distomolar or distodens. A paramolar is a posterior ST located lingual or buccally to a molar. Another classification divides them into supplemental type with normal shape and size or rudimentary type of smaller size and abnormal shape [24]. The ST of rudimentary type can be subclassified as conical of small size and rice form; Tuberculated in the form of barrel and with multiple cusps or tubers; Molariform teeth very similar to premolar or molar and odontomas that are malformations of disorganized dental tissue [9,24,25]. Relatively little is known about the genetic basis, etiology, and molecular mechanisms underlying ST formation. A small number of extra teeth is considered a common anomaly, however usually multiple ST have a genetic component and are thought to represent a third partial dentition [23-29]. Extra teeth show racial variation, exhibit sexual dimorphism and are prominent features in various developmental disorders [9]. ST are more frequent in relatives of affected patients than in the general population.This trait can be transmitted in an autosomal dominant form, with incomplete penetrance, in an autosomal recessive form or linked to the X chromosome [25-29]. Table 1 shows the genes, with literature evidence, involved in the formation of ST [9,25-29]. However, a recent article describes 101 candidate genes selected through bioinformatic programs and criteria [27]. The presence of ST can occur associated with syndromes so it is considered important in early diagnosis for the correct management and informed decision making about medical care and treatment in the long term. A recent study described 8 syndromes with strong evidence of association (Cleidocranial Dysplasia, Familial Adenomatous Polyposis, Trico-Rhino-Falangeal I, Rubinstein-Taybi, Nance-Horan, Opitz BBB/G, Oculo-Facio-Cardio-Dental and Robinow) and two syndromes with evidence suggestive of association with ST (Kreiborg-Pakistani and insulin-dependent diabetes mellituswith acanthosis nigricans) [30]. Interestingly, a recent study has shown that cells derived from ST are a promising source of mesenchymal stem cells for cellular therapy applicable to autoimmune diseases [31].

Developmental Alterations Affecting Tooth Size and Morphology

Abnormalities in tooth size and shape result from disturbances in the morpho-differentiation stage of development, i. e. during cup-to-bell stages [6].

Size

The variation in the size of the teeth is a trait that has normal distribution in human populations, it is variable between ethnicities and sexes. The presence of physically smaller teeth than normal is called microdontia and the presence of larger than average teeth is called macrodontia [9,23-24]. Typically, in either of the two arches only a few teeth are altered in size. Differences in size cannot be considered in isolation, because microdontia is strongly associated with hypodontia and macrodontia with hyperdontia. Women have a higher frequency of microdontia and hypodontia and men have a higher prevalence of macrodontia and hyperdontia [6,9,24]. The generalized microdontia is infrequent and observed mainly in Down syndrome, pituitary dwarfism and other hereditary disorders. The isolated microdontia is more frequent, affecting the maxillary lateral incisors that can present crown in the form of rice and root of normal length. The prevalence is 0.8% to 8.4% and the trait is inherited in an autosomal dominant form with incomplete penetrance [6-10]. Generalized macrodontia is rare and usually only a few teeth are abnormally large in size. It is associated with pituitary gigantism, otodental syndrome, XYY men and pineal hyperplasia with hyperinsulinism. Isolated macrodontia occurs more frequently

bilaterally in incisors, canines and less frequently in second premolars and third molars. A prevalence of 0.1 to 4.3% has been reported [6-10].

Morphology: There are many genetic-based morphological variations of the teeth.

Gemination: Is defined as a single enlarged tooth or united tooth (double) in which the tooth count is normal when the anomalous tooth counts as one [6,10].

Fusion: Corresponds to a single enlarged tooth or two united teeth in which the tooth count reveals an absent tooth when the anomalous tooth counts as one. Gemination or fusion appears in both dentitions, more frequently in the anterior maxillary region (gemination) and mandibular (fusion), being more affected the incisor and canine teeth. The prevalence of double tooth in primary dentition is 0.5 to 2.5%, while in the permanent it is 0.3 to 0.5% [6,10].

Accessory cusps: Such as Carabelli's cusp, which is located on the palatine surface of the mesiolingual cusp of deciduous or permanent upper molars. It occurs in 90% of Caucasians and is rare in Asians. The talon cuspalis an additional cusp located on the surface of an anterior tooth, from the cemento-enamel junction to the incisal margin, are frequent in permanent central and lateral incisor teeth. Dens evaginatus is a cusp-like elevation located in the central cleft of the buccal cusp of incisor or premolar teeth, with a frequency of 1 to 4% in Asians and rare in Caucasians [6-10]. Dens invaginatus (Dens in dente) corresponds to an invagination of a portion of the enamel organ that results in enamel-dentin deeper into the pulp chamber. It has a prevalence ofless than 0.1% and the lateral incisors are the most frequently affected teeth. Shovel- shaped teeth are incisors that have prominent lateral margins and have been described as a frequent variation in natives of America [6-10].

Taurodontism: Corresponds to the enlargement of the body and pulp chamber of a multi-root tooth, with apical displacement of the cameral floor. It affects PeD more frequently, can be uni or bilateral, with a prevalence varyingbetween 0.5 and 46%, and it can occur in isolation or as part of numerous syndromes [6-10,32].

Globodontia: Is a condition in which teeth are shaped like a globe. This rare abnormality is associated with otodental syndrome; it is inherited in an autosomal dominant form, with an unknown prevalence [9,33].

Lobodontia or wolf teeth: Corresponds to an uncommon autosomal dominant abnormality in which teeth are shaped like wolf teeth. The estimated prevalence is 1: 1,000,000 [9, 34-35].

Most of the variation in traits related to tooth size and shape present continuous distribution coincident with a multifactorial model of inheritance, present ethnic variation and association with several hereditary disorders. Genes involved in some of these anomalies are described in table 1 [6-10]. Carabelli cusp, talon cusp, Dens evaginatus and Shovel shaped incisors have relevance in forensic genetics, population genetics and in association with syndromes. Dens invaginatus, gemination and fusion may favor the development of caries, pulpitis and periodontal problems. In addition, they can cause crowding, delayed eruption or ectopic eruption. Taurodontism has anthropological importance and may be associated with syndromes. Globodontia causes malocclusion, increased endodontic lesions and it is a diagnostic feature of otodental syndrome. [6-10,35]

Alterations Affecting the Structure of Dental Hard Tissues

Hereditary Enamel Defects, Amelogenesis Imperfecta (AI)

A heterogeneous group of developmental disorders altering the structure, chemical composition and appearance of the enamel can affect all or almost all primary or permanent teeth, in isolation or as part of syndromes [9,36]. AI are grouped into four clinical phenotypes: hypoplastic, hypocalcified, hypomature and hypomature/hypoplastic with taurodontism. The consideration of secondary enamel traits and inheritance pattern in these four phenotypes categorizes them into 14 different subtypes [9,37]. The estimated frequency of AI in the population ranges from 1 in 8,000 to 1 in 14,000 [9,36-37]. Table 1 summarizes the genetic etiology of the various types of isolated and syndromic AI [37]. Patients with AI present enamel fractures, dentin hypersensitivity, altered masticatory function, need for frequent replacement of obturations, loss of vertical dimension and high prevalence of dentomaxillary abnormalities requiring orthodontic resolution [9,38-39]. The aesthetic aspect of their teeth generates a high psychosocial impact on them; problems of aesthetic dissatisfaction, self-perception and low self-esteem, higher levels of social avoidance, anguish and complex about their teeth, greatly limiting their social life and interaction with their peers [39]. In addition, AI is also associated with other genetic disorders and syndromes. It has been reported that AI is associated with 23 autosomal dominant syndromes, 45 autosomal recessive inheritance syndromes and 12 chromosome X-linked inheritance conditions, increasing the list of genes possibly involved in AI [40]. Hereditary defects of dentin. These defects include two entities: Dentinogenesis Imperfecta (DI) and Dentin Dysplasia (DD) [5,9,36].

Dentinogenesis Imperfecta

Is an autosomal dominant disease characterized by severe hypomineralization and altered dentin structure, caused by mutations in the dentin sialo-phosphoprotein (DSPP), from which sialo-dentin protein (DSP), dentin glycoprotein (DGP) and dentin phosphoprotein (DPP) are formed, playing important roles in tissue mineralization [5,9,36]. The recent proposed classification, based on molecular analysis of the DSPP gene, includes three types of DI: mild form (previously considered DD type II), moderate (before DI type II) and severe (before DI type III) [41]. Epidemiological data indicate that DGI has a prevalence of 1: 6,000 to 1: 8,000 [5,9,36], and it is caused by genetic variants of the DSPP gene, the main non-collagenous protein in the dentin matrix [5,9,36]. Teeth are small, colored blue-gray or amber and opalescent. The enamel is detached from the underlying hypomineralized dentine that is exposed and rapidly wears through attrition. Radiographically, bulbous crowns are observed due to cervical constriction, short and thin roots, tooth mobility, total or partial pulpal obliteration, and increased periodontal disease in the absence of caries [36,41]. Association of DI with several syndromes such as Osteogenesis Imperfecta, Ehlers-Danlos and Goldblatt and Schimke immuno-osseous dysplasia has been described [36].

Dentin Dysplasia

Is a hereditary defect characterized by normal-looking crowns and short roots in both dentitions.Pulp cavities are small in size and associated with periapical radiolucencies and obliterated pulp chambers [36,41]. The most up-to-date classification distinguishes one clinical entity; dysplasia of the root dentin, formerly called DD type I. This defect is extremely rare, with a prevalence of 1: 100,000 and affects both dentitions [41]. DD is inherited in an autosomal dominant form, with complete penetrance, although cases with autosomal recessive inheritance have

also been described [42]. Table 1 shows the genes involved in DD [35,36,41]. Clinically, teeth look normal, the first sign of disease is tooth mobility leading to premature exfoliation, roots are short or absent, fused, with a conical apical aspect (taurodonts) and the pulp is replaced by dentin-like mineralized tissue. Periapical lesions and periodontal disease are frequent [36,41].

Defects of Enamel and Dentin Development of Uncertain Etiology

In this group are included enamel development defects (EDD) such as hypoplasias and opacities, regional odontodysplasia, molar incisive hypomineralization (MIH), molar incisive malformation (MIM) and dental fluorosis. Evidence of the genetic component implied in these conditions has begun to accumulate, and for now they respond to a model of continuous distribution of multifactorial etiology [6-10,43,44].

Developmental Alterations Affecting the Eruption of the Teeth

Dental eruption is a temporally and locally regulated process that requires bone resorption and deposition. It corresponds to the movement of a tooth from its site within the alveolar bone to its functional position in the oral cavity [10,45,46]. Among the alterations in the chronology of eruption are: 1) Early dental emergence, which occurs when a tooth erupts before the third month of life (natal or neonatal tooth), is very rare and has genetic influence; 2) Late eruption of the primary dentition, which occurs when no tooth has erupted at the 13th month of life; 3) Early eruption in PeD, corresponding to eruption before full root formation, more frequent when the temporal tooth is prematurely lost; 4) Late PeD eruption, which occurs due to loss of the temporary tooth with insufficient root development of the permanent successor, temporal ankylosis or late formation of the permanent germ; 5) Primary eruption failure (PEF) is the localized failure of PeD eruption without any other systemic condition present [9,10]. It affects permanent molars uni or bilaterally that are completely formed and do not reach the occlusal plane due to a primary defect in the mechanism of eruption. There are isolated PEF types with familial and non-familial forms [45,46].The prevalence of alterations of the eruption is variable. Natal or neonatal teeth occur in about 1:3,000 children, mainly affecting the incisors. Failure of eruption of first and second molars is rare, with an estimated prevalence of 0.01% for the permanent first molar and 0.06% for the second molar [9,45,46]. PEF is an autosomal dominant disorder due to mutations in the parathyroid hormone receptor 1 (PTH1R) gene. However, an analysis of the molecular mechanisms of the eruption process reveals other obvious candidate genes (Table 1) [10,45,46]. As in other dental disorders, eruption abnormalities are also associated with syndromes. Natal teeth are observed in Ellis-Van-Creveld, Congenital Pachyonyquia type 1 and Hallermann-Streiff syndromes. Generalized delayed eruption of both dentitions is present in Down's syndrome, gingival fibromatosis, hypothyroidism, and childhood hypopituitarism. Delayed eruption of PeD is associated with Creidocranial dysplasia, among other syndromes. [45,46].

Process / anomaly	Gene name	Gene name	Gene name
1. Tooth Development	ACTBA	FGF2	P63
1.1. Odontogenesis in General	ACTRIIA	FGF20	PAX3
	ACVR1	FGF3	PAX6
	ACVR1B	FGF4	PAX9
	ACVR2A	FGF5	PDGFA

	ACVR2B	FGF6	PDGFC
	ALX1	FGF7	PDGFRA
	AXIN2	FGF8	PDGFRB
	BARX1	FGF9	PITX2
	BMP2	FGFR1	PRRX1
	BMP4	FGFR2	PRRX2
	BMP5	FGFR3	PRX1
	BMP6	FOXI3	PRX2
	BMP7	FST	PTCH1
	BMPR1A	GAS1	PTHR1
	BMPR1B	GLI1	RUNX2
	BMPR2	GLI2	RUNX3
	CAVI	GLI3	SHH
	CBLB	HOXA2	SHOX2
	CDKN1A	HOXD10	SMAD2
	DKK1	IFT88	SMAD6
	DKK4	IGF1R	SMO
	DLX1	IKKA	SOSTDC1
	DLX2	IKKR	SP6
	DLX3	IRAK3	SPRY2
	DLX5	IRF6	SPRY4
	EDA	LEF1	TAB2
	EDAR	LHX6	TBX10
	EDARADD	LHX8	TFAP2A
	EGF	LTBP3	TFAP2C
	EGFR	MET	TGFA
	EPHB3	MSX1	TGFB3
	ERBB2	MSX2	TGFBR2
	ERBB3	NOG	TP73L
	ERBB4	NR2F1	TRAF6
	EVC	NTRK3	WNT10A
	FGF1	OSR2	WNT10B
	FGF10	P21	-
2. Number Of Teeth			
2.1. Non-syndromic Tooth Agenesis	KDF1	EDARADD	NFATC3
	AXIN2	FAM65	PAX9 (STHAG 3)
	BMP2	GREM2 (STHAG 9)	SMOC2
	BMP4	HYD2 (STHAG 2)	TSPEAR
	CDH23	KREMEN1	WNT10A (STHAG 4)
	DKK1	LRP6 (STHAG 7)	WNT10B (STHAG 8)
	EDA (STHAG X1)	LTBP3 (STHAG 6)	-
	EDAR	MSX1 (STHAG 1)	-
2.2 Syndromic Tooth Agenesis	ADAMTS2	GJA1	P53

	ANTXR1	GLI3	P63
	APC	GRHL2	PAX3
	AXIN2	HOXB1	PHGDH
	BCOR	IFT121	PITX2
	COL1A1	IFT122	POLR3A
	COL1A2	IKBKG	POLR3B
	COL3A1	IKKγ	PORCN
	CREBBP	IRF6	PRX1
	CXORF5	JAG1	PRX2
	DLX1	KDM6A	PVRL1
	DSP	KIF3A	RECQL4
	DTDST	KMT2D	RIEG2
	EDA	KREMEN1	RSK2
	EDAR	KRT17	SHH
	EDARADD	LHX6	SLC25A21
	ERCC8	LHX8	SMAD2
	EVC1	LTBP3	SMO
	EVC2	MKKS	TBX22
	EYA1	MMP1	TBX3
	FAP2B	MMP13	TCOF1
	FGD1	MMP20	TFAP2B
	FGF10	MMP9	TGFB
	FGFR1	MSX1	TGFB3
	FGFR2	NECTIN1	TSPEAR
	FGFR3	NEFL	UBR1
	FLNA	NEMO	WNT10A
	FLNB	NF-KB	WNT5A
	FOXC1	NSD1	-
	FUZ	OFD1	-
2.4 Supernumerary Teeth (ST)	APC	FGF4	PAX6
	BMPR1A	FGFR2	PAX9
	CDH1	FOXN1	PAXSEY
	CHD8	GAS1	PDGFRB
	COL3A1	GCM2	PLOD
	CRE1	GLA	PTPN11
	CREBBP	GSK3B	R-SPONDIN2
	CTNNB1	IFT88	RECQL4
	EDA	IKBKG	ROR2
	EDAR	IL11RA	RUNX2
	ERTM	LPR4	SATB2
	EVC	LPR5	SOSTDC1
	EVC	LPR6	SOX2
	EVC2	MNX1	SPRY2

	EYA1	MSX1	SPRY4
	FAM20A	NEMO	TNXB
	FAM20B	NHS	TRPS1
	FGF10	OFD1	-
	FGF3	OSR2	-
3. Shape of the Teeth			
	ANKRD11	EVC	PCNT
	AXIN2	EVC2	RECQL4
	BCOR	FGF3	SMARCAL1
	CACNA1S	GREM2	SMOC2
	CREBBP	IKBKB	SOSTDC1
	DLX3	IKBKG	TRAF6
	EDA	IKKA	WNT10A
	EDAR	IKKR	WNT5A
	EDARADD	IKKγ	-
4. Tooth Structure			
Enamel	ACP4	ENAM	MMP20
4.1 Non-syndromic Amelogenesis Imperfecta	AMBN	FAM20A	ODAPH
	AMELX	FAM83H	RELT
	AMTN	GPR8	SLC24A4
	CLDN16	ITGB6	SP6
	CLDN19	KLK4	STIM1
	CNNM4	LAMA3	TP63
	COL17A1	LAMB3	WDR72
4.2 Syndromic Amelogenesis Imperfecta	AIRE	FAM20C	OCRL1
	ALDH3A2	FGF23	PDZD7
	ATR	FOXC1	PEX1
	CLDN16	GALNS	PEX6
	CLDN19	GALNT3	PITX2
	CNNM4	GLB1	ROGDI
	COL17A1	GPR98	SLC10A7
	COL7A1	HSD17B4	SLC13A5
	CREBBP	KIND1	SLC4A4
	DLX3	LAMA3	TBCE
	ERCC8	LAMB3	TP63
	EVC1	LAMC2	TRPM
	EVC2	LTBP3	OCRL1
	FAM20A	NHS	PDZD7
Dentin			
4.3 Dentinogenesis Imperfecta	DSPP		
4.4 Dentin Dysplasia	MT1-MMP	NOTUM (Mouse)	SMOC2
	SSUH2	VPS4B	-
5 Tooth Eruption			

5.1 Failure Primary Eruption	ALPL	IDS	PORCN
	ASB	IKBKG	POSTN
	CA2	IL11RA	PTH1R
	CCL2	IL6ST	PTH1R
	CICN5	LAD3	PTHLH
	CLCN7	LEMD3	RANKL
	COL1A1	LONP1	RANKR
	COL1A2	MiR-31	SATB2
	CSF1	NSD1	SFRP1
	CTSC	OLEKHM1	SLC4A2
	CTSK	OPG	TCIRGI,
	DMP1	OSTM1	TNFa
	FGF23	POLR3A	VEGF1

Table 1: List of genes associated with developmental defects that alter the number, size, shape, structure and eruption of the teeth.Those genes in which mutations have been described in mouse models or human beingsare annotated. Note that some genes are involved in isolated and syndromic developmental disorders. This table is based on references [6,10,14-16,23,28,32,37,40,45-51].

Conclusions

The presence of dental development abnormalities in patients, not only generates diverse clinical complications, but also impacts the aesthetic aspect of their teeth and produces a high psychosocial impact on them; problems of aesthetic dissatisfaction, self-perception and low self-esteem, higher levels of social avoidance, anguish and complex about their teeth, greatly limiting their social life and interaction with their peers. In addition, most of the alterations in tooth development can occur in isolation or associated with syndromes, therefore the presence of any of these abnormalities in patients can be used preventively as a possible marker of syndromic association, which should be exhaustively studied.

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Conflict of Interest

The authors deny any conflicts of interest related to this manuscript.

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