Molecular Genetic Mechanisms of Congenitally Missing Teeth

Zhuan BIAN[1], Wei YIN[1], Xiao Qian YE[1]

Abstract: *Congenital agenesis of permanent and/or primary teeth is one of the most common orofacial developmental disorders. Although environmental factors can also affect tooth agenesis, genetic factors play a more important role. It can be classified into nonsyndromic and syndromic hypodontia.* MSX1, PAX9, DLX1, DLX2, Activin beta-A, Activin receptor types IIA *and* IIB, *and* SMAD2 *have been considered related to the former. Syndromic congenitally missing teeth is related to ectodermal dysplasias, Van der Woude syndrome and other syndromes. In this article, we will review the molecular genetic mechanisms of congenitally missing teeth.*

Key words: *congenitally missing teeth, hypodontia, mechanisms, molecular genetics*

Congenital agenesis of permanent and/or primary teeth is one of the most common orofacial developmental disorders. Most patients have obvious family history. It can be inherited as autosomal dominant/recessive and X-linked inheritance. In view of the number of teeth missing, it has been classified into hypodontia (missing six teeth or fewer), oligodontia (missing more than six teeth), and anodontia (missing all teeth)[1]. Based on whether it is accompanied by other symptoms, it has been divided into nonsyndromic congenitally missing teeth and syndromic congenitally missing teeth. The latter includes ectodermal dysplasias, Van der Woude syndrome (VWS) and other syndromes.

Nonsyndromic Congenitally Missing Teeth

Clinical features

Nonsyndromic congenitally missing teeth, with an overall incidence of 1.6 to 9.6%[2], is a lack of teeth not caused by extraction or injury, unaccompanied by other symptoms. It is well-known for phenotypic heterogeneity, as there is great variation in the number and position of missing teeth. The most common positions are the third molar, second premolar and maxillary lateral incisor[1]. Furthermore, the configuration of residual teeth is usually abnormal.

He-Zhao deficiency is a special type of nonsyndromic congenitally missing teeth, characterised by normal primary dentition and high prevalence of permanent tooth agenesis without any other abnormalities.

In general, the lateral permanent teeth tend to be present rather than the third maxillary and mandibular molars or the central maxillary and mandibular teeth. However, missing second premolars and maxillary lateral incisors is more common than for other teeth. The most severely affected patients exhibit anodontia before reaching their forties[3].

Molecular genetic mechanisms

Genetic factors play an important role in missing teeth, although environmental factors, such as physical and chemical factors and radiation, can also be causes (Fig 1)[4]. From genetic studies, it is evident that hypodontia has a heterogeneous trait for which several mutated genes are responsible. Animal experiments have revealed over 200 genes related to odontogenesis[5]. Genes involved in epithelial-mesenchymal interactions, growth factors and transcription factors may be candidates. In humans, *MSX1*,

1 Key Laboratory of Oral Biomedical Engineering of Ministry of Education, Hospital and School of Stomatology, Wuhan University, Wuhan, P.R. China.

Corresponding author: Dr Zhuan BIAN, Key Laboratory of Oral Biomedical Engineering of Ministry of Education, Hospital and School of Stomatology, Wuhan University, Luoyu Road 237, Wuhan 430079, P.R. China. Tel: 86-27-87647443; Fax: 86-27-87647443. E-mail: bz@whuss.com

This study was supported by grant from the National Natural Science Foundation of China (No.30500562).

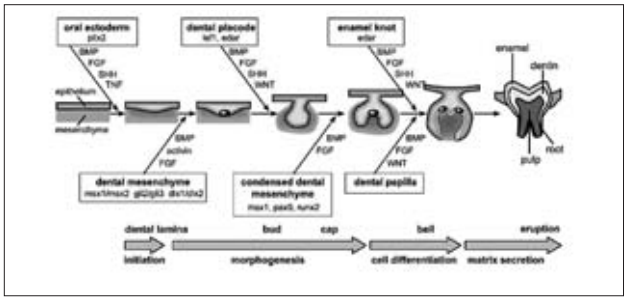

Fig 1 Tooth development is regulated by conserved signal pathways (FGF, BMP, SHH, WNT and TNF). The signals mediate interactions between the oral ectoderm and mesenchyme and regulate the expression of key transcription factors (shown in the boxes). Mutations of the transcription factors in this figure cause tooth agenesis in mice, and most of them are associated with dental defects in humans[4].

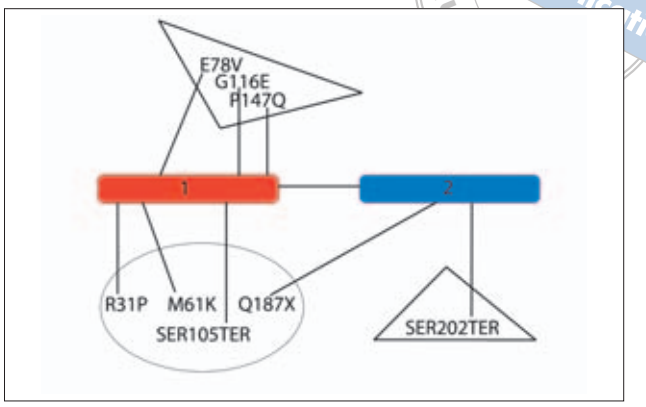

Fig 2 Mutation distribution in MSX1. The oval, top triangle and bottom triangle indicate mutations found in nonsyndromic congenitally missing teeth, cleft lip with or without cleft palate, and Witkop syndrome respectively.

PAX9, *DLX1*, *DLX2*, *Activin beta-A*, *Activin receptor types IIA* and *IIB*, and *SMAD2* are considered to be involved in nonsyndromic congenitally missing teeth, but only *MSX1* and *PAX9* mutations have been detected in the patients[6].

MSX1

MSX1, homologous with the mouse homeobox gene *Hox7*, locates at 4p16.1. It has two exons that encode 297 amino acids. MSX1, a non-clustered homeobox protein, acts as a transcript inhibitor through interactions with homeoprotein and nucleus transcription. It plays an essential role in craniofacial development, especially tooth development.

In mice, *Msx1* expresses in the dental mesenchyme, including the dental papilla throughout the lamina, bud, cap, and bell stages of odontogenesis[7]. Similarly, *MSX1* is restricted to the dental papilla mesenchyme of the primary tooth germ at the cap stage in human. Both the incisor and the premolar exhibit a similar expression pattern. It is interesting to note that at the bell stage, while remaining in the dental papilla cells, *MSX1* is also seen in the inner enamel epithelium at a very high level in incisors and premolars. At the late differentiation stage, similar to the expression pattern of *BMP4*, *MSX1* transcript is detected in the odontoblasts and ameloblasts of a premolar that had been grafted and cultured in the kidney capsule for 2 months[8].

Many mutations, including missense mutation, nonsense mutation and frameshift mutation, have been identified in autosomal dominant congenitally missing teeth pedigrees (Fig 2). Loss-of-function of *MSX1* may result from haploinsufficiency or dominant-negative mechanism. Because homeoprotein of *MSX1* is expected to interact with other transcription factors and bind DNA, mutation in this area will functionally inactivate partner proteins as well as perturb homeoprotein/DNA interactions[9]. Moreover, fluorescence *in situ* hybridisation analysis suggests that lack of one copy of *Msx1* is associated with oligodontia[10].

However, it is worth considering that *MSX1* mutation can also be found in cleft lip with or without cleft palate and Witkop syndrome[11]. *Msx1*-knockout mouse has a similar phenotype, as tooth development is disrupted and nail plates are defective and thinner than those of their wildtype littermates.

PAX9

PAX9 is essential to tooth development, as indicated by its expression pattern, the mouse phenotype of *Pax9*$^{-/-}$ and the association of agenesis of permanent dentition with *PAX9* mutations in humans[12,13]. In mouse embryos, *Pax9* is an early marker of tooth development before the expression of other tooth signalling genes. High levels of *Pax9* expression are subsequently maintained throughout the initiation, bud and cap stages and are down-regulated at the bell stage.

Mesenchymal expression of Pax9 is initially regulated by antagonistic signals of Bmp4 and Fgf8. Pax9 is likely to mediate its tooth-specific functions through interaction with other proteins, like partnership between the Pax9 paired domain protein and the Msx1 homeoprotein in regulating gene expression in dental mesenchyme[6].

So far, 15 mutations, including missense mutation, nonsense mutation and frameshift mutation, have been confirmed in nonsyndromic congenitally missing teeth pedigrees. Most of them locate in the paired box domain (Table1).

PAX9 is a dosage-sensitive gene for its expression level

Table 1 *PAX9* mutations

Exon	Amino acid change	Mutation type
2	219insG	Frameshift
2	K114Stop	Nonsense
4	793insC	Frameshift
2	K91E	Missense
2	L21P	Missense
2	175ins288bp	Frameshift
2	G51S	Missense
2	R28P	Missense
2	R26W	Missense
1	c.1A>G	No transcript
2	109insG	Missense
2	619_621delA Tins 24 bp	Missense
2	139C>T	Missense
2	I87F	Missense
	Gene locus deletion	No transcript

has a direct influence in mammalian dental patterning. Haploinsufficiency will results in a severe form of tooth agenesis: a >57 kb deletion encompassing the *PAX9* locus results in a severe hypodontia involving agenesis of all primary and permanent posterior teeth. Relatively milder phenotypes may be the result of a defective allele that generates an aberrant protein which acts in a dominant-negative manner or has a novel function[14]. This, however, fails to fully explain the mechanisms underlying other disease-causing mutations that result in less severe and variable phenotypes. It is possible that the mutant allele may be hypomorphic. The combined activities of the wild type and mutant alleles cannot reach the threshold level necessary for normal tooth development.

BMP4

Bone morphogenetic protein 4 (BMP4), a member of the transforming growth factor (TGF) superfamily, constitutes one component of the inductive signals that transfer tooth inductive potential from dental epithelium to mesenchyme[15]. *Bmp4* expression is first observed in molars in the dental lamina epithelium, and then shifts to the dental mesenchyme, coincident with the shift in tooth developmental potential between tissue layers. In addition, *Bmp4* can induce morphological changes in dental mesenchyme[15,16].

Msx1 and *Pax9* are essential for the establishment of the odontogenic potential of the mesenchyme through the maintenance of mesenchymal *Bmp4* expression. Tooth development of *Msx1* mutant mice arrest in bud stage, which may be the result of affecting *Bmp4* and *Fgf3* expression. Furthermore, the ceasing tooth development of double heterozygous *Pax9/Msx1* mice can be rescued by transgenic expression of *Bmp4*[17].

Bmp4 expression is reduced in the *Msx1* mutant tooth mesenchyme but is preserved in *Msx1* mutant epithelium[18,19]. This phenomenon indicates that *Msx1* is required for the expression of *Bmp4* in the dental mesenchyme and therefore *Bmp4* functions downstream of *Msx1* in the dental mesenchyme. On the contrary, epithelial *Bmp4* expression does not require *Msx1* for its expression and therefore acts upstream of *Msx1*. In addition, *Bmp4* can induce the expression of *Msx1* and itself in the dental mesenchyme[15]. Pax9 appears to be integrated with Msx1 in a feedback loop to regulate Bmp4 expression in the mesenchyme. However, in *Msx1* mutant dental mesenchyme, *Bmp4* cannot induce its own expression. Furthermore, addition of recombinant *Bmp4* to chemically defined media partly rescues the *Msx1* mutant tooth bud phenotype to the cap stage of odontogenesis[19], further substantiating the view that mesenchymal *Bmp4* functions downstream of *Msx1* and suggesting that mesenchymal *Bmp4* acts back upon the dental epithelium to mediate the reciprocal epithelial-mesenchymal interactions that occur during tooth morphogenesis[20]. However, no mutation has been identified in *BMP4*.

Locus for He-Zhao deficiency[21]

Genotype and haplotype analysis identified He-Zhao deficiency locus within a 5.5 cM region flanked by markers D10S604 and D10S568 on chromosome 10q11.2. Several genes in this area may be the causative gene, including *Dickkopf-1* (*Dkk-1*), *PRKG1B* and a *KOX* zinc finger gene cluster.

Relationship between phenotype and genotype

It is well-known that there is a relationship between the phenotype and genotype of nonsyndromic congenitally missing teeth. The incisors and mandibular molars of *Activin beta-A* mutant mouse embryos fail to develop beyond the bud stage. Development of maxillary molars, however, is normal in the mutants. *Activin receptor types IIA* and *IIB* and *Smad2* mutant mice have similar phenotypes[22].

In humans, incisor-premolar hypodontia (IPH) is one of the most common types of autosomal dominant inherited hypodontia. The mean missing number of teeth in IPH is 2.3. The most frequently missing teeth are mandibular second premolars, maxillary second premolars and maxillary lateral incisors, but not third molars. Primary dentition is not affected. Calculated penetrance is up to 97%. The shape of the residual teeth may be abnormal. The genetic cause for this condition has not been found, but *MSX1*, *MSX2*, *EGF*, *EGFR* and *FGF-3* have been excluded[23-25].

Table 2 Difference between type and causative genes of human and mouse agenesis

Gene	Type of human tooth agenesis	Type of mouse tooth agenesis
MSX1/Msx1	Premolars and third molars	Incisors, premolars and molars
PAX9/Pax9	Molars	Mandibular incisors and third molar
DLX1 and *DLX2/Dlx-1* and *Dlx-2*	None	Maxillary molars
Activin beta-A, activin receptor types IIA and *IIB, SMAD2/Smad2*	None	Incisors and mandibular molars
FGF8/Fgf8	None	All but mandibular incisors

Comparison of human and mouse tooth agenesis

The phenotypes seen in mouse mutants overlap with those of humans carrying mutations in the counterpart genes. These indicate that tooth development in mice and humans not only shares many similarities in the morphological processes, but also that they may also have similar molecular mechanisms[8]. However, there are still some subtle differences (Table 2).

Syndromic congenitally missing teeth

Congenitally missing teeth is related to a great number of syndromes, including ectodermal dysplasia and VWD.

EDA, *EDAR* and *EDARADD*

Ectodermal dysplasia is a group of complicated disorders comprising more than 200 clinical combinations[26]. As well as the absence of some teeth and unusual tooth shape, patients also have congenital defects of one or more ectodermal structures and their appendages, such as hair and sweat glands. Most are X-linked and autosomal recessive/dominant forms, although there are some sporadic cases. *EDA* is mainly responsible for the X-linked form (XED). For mice, *Crinkled* (*Cr*) and *Downless* (*Dl*) genes are related to autosomal disorders. The protein is a type II membrane protein that can be cleaved by furin to produce a secreted form. The encoded protein, which belongs to the tumour necrosis factor (TNF) family, acts as a homotrimer and may be involved in cell–cell signalling during the development of ectodermal organs. The human homologies are *EDARADD* and *EDAR*. *EDARADD* is a death domain adaptor that interacts with the death domain of *EDAR* and links the receptor to downstream signalling pathways (Fig 3)[27]. *EDARADD* and *EDAR* are co-expressed in epithelial cells during the formation of hair follicles and teeth. Overexpression of *EDARADD* in HEK293T cells resulted in an NF kappa-B (NF-κB) reporter gene activation in a dose-dependent manner.

For different alternative splicing, *EDA* has at least nine transcripts. *EDA-A1* encodes a 391-amino acid protein with a domain similar to TNF at the C terminus. EDAR, which is activated by EDA-A1, only binds to EDA-A1 and uses EDARADD as an adaptor to build an intracellular signal-transducing complex[28], while XEDAR only binds to EDA-A2, which deletes two amino acids, Glu308 and Val309, compared with EDA-A1. Dl can trigger NF-κB through the NEMO protein[29]. Similarly, EDA-A1 and EDA-A2 can activate NF-κB-promoted transcription after binding to their receptors. These indicate XED may result from impaired NF-κB signalling.

Heretofore, 91 *EDA* mutations have been found in XLHED, most of which are missense mutations (Table 3). These centralise in four clusters: the junction of the transmembrane and the extracellular domain, the protease recognition site, the trimerising collagen-like domain, and the TNF homology domain.

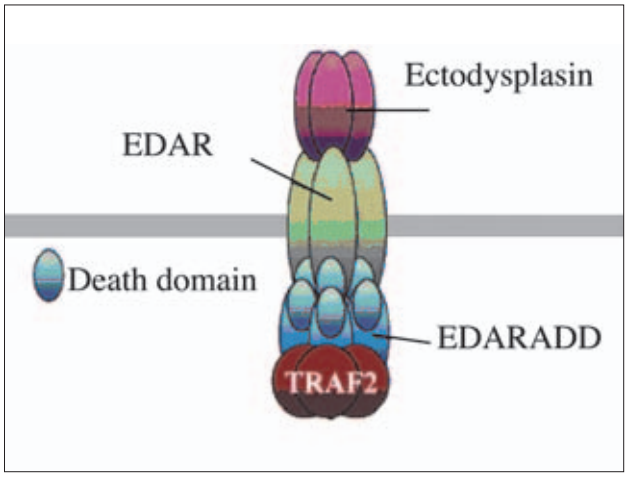

Fig 3 The interaction between Ectodysplasin, EDAR and EDARADD[27].

Table 3 *EDA* **mutations**

Exon	Amino acid change	Mutation type
1	Q23X	Nonsense
1	31DelC	Frameshift
1	H54Y	Missense
1	Del Ex1	
3	R153C	Missense
3, 4	Del Ex3 + 4	
5	G207R	Missense
5	G224A	Missense
5	599-600 Ins C	Frameshift
6	R244X	Nonsense
7	H252Y	Missense
8	G269V	Missense
9	Y343C	Missense
9	I360F	Missense
9	T378P	Missense

P63

P63 has prominent gene pleiotropism. It can lead to EEC, AEC, LMS, ADULT, RHS and EE syndromes, which together are also called P63 syndrome[30]. All of the syndromes lead to missing teeth. The penetrance is from 29 to 100%.

P63 gene, a homology of the archetypal tumour suppressor gene *P53*, is a new member of P53 family. It locates at 3q27-3q29 and has two promoters leading to six different transcripts. The second promoter is in an intron that is 30 kb away from the first promoter. The main structure of *P63* includes a transactivation domain, DNA binding domain, tetramerisation domain and sterile alpha motif (SAM)[31,32] (Fig 4A). It plays a significant role in the development of ectoderm since it expresses in the progenitor cells of many epithelial tissues, particularly in the apical ectodermal ridge of the limb bud, branchial arches and the epidermal appendages. In *p63*$^{-/-}$ mice, the skin is absent and newborn animals die from dehydration shortly after birth. Besides, these mutant mice exhibit defects in structures dependent on epidermal–mesenchymal interactions such as hair follicles, teeth primordia and mammary glands as well as cleft palate and truncated limbs. These features are identical to patients with *P63* mutations[33].

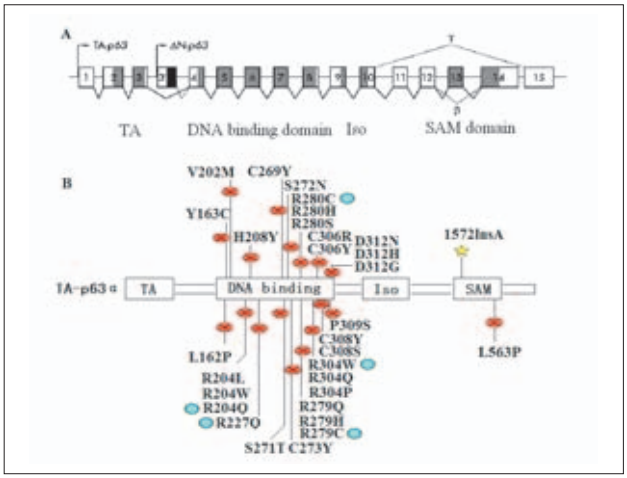

Fig 4 *P63* gene structure, transcripts and mutation sites. (A) The diagram of the intron-exon structure shows the two transcription initiation sites and alternative splicing routes. The main structure of *P63* contains transactivation domain (TA), DNA binding domain, tetramerisation domain (ISO) and SAM domain. (B) Mutation distribution in *P63* of EEC (ectrodactyly, ectodermal dysplasia, and cleft lip/palate) patients. The red ovals and yellow stars represent the missense mutations and frameshift mutation respectively. The blue circles denote the mutational hotspots of *P63*.

Many mutations in *P63* have been found to relate to P63 syndrome (Fig 4B). Mutations in DNA binding domain will affect binding of P63 to DNA leading to low transcript activity. Sterile alpha motif exists in many signal proteins that take part in development and differentiation. Therefore, it plays a significant role in interactions among proteins and tissue development and differentiation. Mutations in sterile alpha motif can inhibit specified interactions among proteins.

IRF6

VWS is an autosomal dominant disorder with incidence of 1/34,000. Lower lip pits, cleft lip with or without cleft palate, and hypodontia are the main clinical features. Its penetrance is 95 to 100%, but expressivity varies highly. *Interferon regulatory factor-6* (*IRF6*) is the causative gene. *IRF6* belongs to a family of 9 transcription factors that share a highly conserved helix-turn-helix DNA-binding domain and a less conserved protein-binding domain.

More than 70 mutations in *IRF6* have been detected in VWS (Fig 5). These mutations are almost evenly divided between the DNA-binding domain and protein-binding domain, and lead to loss of function of the IRF6 protein. Furthermore, mutations in *IRF6* can also induce popliteal pterygium syndrome (PPS) with dominant-negative effect. PPS has a similar orofacial phenotype, together with skin and genital anomalies. Put simply, haploinsufficiency of *IRF6* disrupts orofacial development[34].

The occurrence of cleft lip/palate and cleft palate within the same family and the recurrence risk of less than 40% for cleft palate among descendants with VWS suggests that the development of clefts in this syndrome

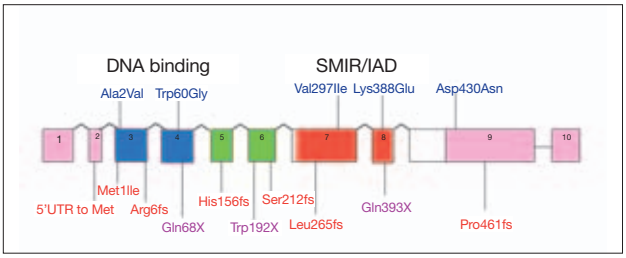

Fig 5 The structure of the *IRF6* gene. Exons are drawn to scale except for exon 9, which is longer than shown. The brackets connecting the exons represent spliced introns, and the line between exon 9 and 10 represents an unspliced intron of 1,621 nt that is present in the most common 4.4-kb *IRF6* transcripts. The untranslated portions are in pink. The DNA-binding domain is blue, and the SMIR/IAD protein-binding domain is red. The amino acid changes written in red, purple and blue represent frameshift mutations, nonsense mutations and missense mutations respectively.

is influenced by modifying genes at other loci. By linkage analysis in a large Brazilian VWS family, a gene at 17p11.2-p11.1 was shown to enhance the probability of cleft palate[35].

PITX2

Reiger syndrome is a dominantly inherited disorder characterised by hypodontia, malformation of the anterior chamber of the eye and umbilicus abnormity. Two suspicious loci, 4q25[36] and 13q14[37], and one gene, *PITX2*, have been identified as related to these abnormities. Some frameshift mutations and missense mutations in *PITX2* have been found in Reiger syndrome patients.

PITX2 is a member of the *PITX/RIEG* family of bicoid-related homeobox genes. In mice, *Pitx2* expresses in the presumptive dental epithelium before tooth formation and remains in the dental epithelium throughout the entire tooth developmental process. The expression pattern of *PITX2* in the developing human tooth germ is identical to that in mice. Both in the incisor and premolar, PITX2 expression is detected only in the dental epithelium at the late bud stage, the cap stage, and the bell stage. In the well-differentiated tooth, the expression of PITX2 is restricted to the ameloblasts. These results support a role for *PITX2* in the development of dental epithelium and differentiation of enamel organ in the human tooth[38].

Pitx2$^{-/-}$ mice have defective development of the mandibular and maxillary facial prominences, regression of the stomodeum and arrested tooth development. Fgf8 expression is absent, and Bmp4 expression is expanded in the branchial-arch ectoderm[39].

AXIN2

Axin2, containing regulator of gene protein (RGS)-signalling, glycogen synthase kinase (GSK)-binding, beta-catenin-binding, and Dishevelled (Dsh) domains, is essential in regulation of the stability of beta-catenin in the Wnt signalling pathway. It organises a multiprotein complex of adenomatosis polyposis coli (APC), beta-catenin, GSK3B, and itself, which leads to the degradation of beta-catenin. At first, *AXIN2* was considered as the pathogenesis of colorectal cancer (CRC), as for 11 of 45 CRC patients AXIN2 mutations were detected and its expression was higher than normal[40]. Now it is regarded as involved in oligodontia and CRC syndrome, which is characterised by severe permanent tooth agenesis and CRC. Most patients are missing at least eight permanent teeth or have anodontia. *AXIN2* mutation detected in such patients, and in those with severe tooth agenesis, strongly supports this conclusion[41]. Mutated *AXIN2* stabilises beta-catenin and activates beta-catenin/T-cell factor signalling. It has been suggested that complex control of Wnt signal activity is necessary for normal tooth development. Whether or not tooth agenesis is an indicator of cancer susceptibility requires further verification.

In addition, Incontinentia pigmenti (IP), Witkop syndrome, Mobious syndrome and Williams syndrome, among others, are accompanied by congenitally missing teeth.

Outlook

Congenitally missing teeth is a complicated group of disorders for which the delicate mechanism is still unclear. So far only a few related genes have been identified. The relationships among these genes on the molecular level remains unknown. Animal models have suggested that many genes are involved in missing teeth. Whether their homologies in humans relate to congenitally missing teeth remains to be studied. The signal pathway in the epithelium and mesenchyme also needs to be illuminated, as this will help to understand how missing teeth occurs. Further studies on tooth development and missing teeth may provide new information to satisfy the need for a disease gene network using probability frameworks. From this, we can hope to find the factors that play a critical role in the disease.

References

1. Vastardis H. The genetics of human tooth agenesis: new discoveries for understanding dental anomalies. Am J Orthod Dentofacial Orthop 2000;117:650-656.

2. McKusick VA. Mendelian Inheritance in Man. Catalogs of Human Genes and Genetic Disorders. 12th edition. Baltimore, MD: Johns Hopkins University Press, 1998.
3. Wang H, Zhao S, Zhao W, Feng G, Jiang S, Liu W, Li S, Xue H, He L. Congenital absence of permanent teeth in a six-generation Chinese kindred. Am J Med Genet 2000;90:193-198.
4. Thesleff I. The genetic basis of tooth development and dental defects. Am J Med Genet A 2006;140:2530-2535.
5. Mostowska A, Kobielak A, Trzeciak WH. Molecular basis of non-syndromic tooth agenesis: mutations of MSX1 and PAX9 reflect their role in patterning human dentition. Eur J Oral Sci 2003;111:365-370.
6. Kapadia H, Mues G, D'Souza R. Genes affecting tooth morphogenesis. Orthod Craniofac Res 2007;10:105-113.
7. MacKenzie A, Leeming GL, Jowett AK, Ferquson MW, Sharpe PT. The homeobox gene *Hox7.1* has specific regional and temporal patterns during early murine craniofacial embryogenesis, especially tooth development *in vivo* and *in vitro*. Development 1991;111:269-285.
8. Lin D, Huang Y, He F, Gu S, Zhang G, Chen Y, Zhagn Y. Expression survey of genes critical for tooth development in the human embryonic tooth germ. Dev Dyn 2007;236:1307-1312.
9. Vastardis H, Karimbux N, Guthua SW, Seidman JG, Seidman CE. A human *MSX1* homeodomain missense mutation causes evidence tooth agenesis. Nature Genet 1996;13:417-421.
10. Nieminen P, Kotilainen J, Aalto Y, Knuutila S, Thesleff I. *MSX1* gene is deleted in Wolf-Hirschhorn syndrome patients with oligodontia. J Dent Res 2003;82:1013-1017.
11. Jumlongras D, Bei M, Stimson JM, Wang WF, DePalma SR, Seidman CE, Felbor U, Maas R, Seidman JG, Olsen BR. A nonsense mutation in *MSX1* causes Witkop syndrome. Am J Hum Genet 2001;69:67-74.
12. Stockton DW, Das P, Goldenberg M, D'Souza RN, Patel PI. Mutation of *PAX9* is associated with oligodontia. Nat Genet 2000;24:18-19.
13. Peters H, Neubüser A, Balling R. Pax genes and organogenesis: *Pax9* meets tooth development. Eur J Oral Sci 1998;106(suppl):38-43.
14. Kist R, Watson M, Wang X, Cairns P, Miles C, Reid DJ, Peters H. Reduction of *Pax9* gene dosage in an allelic series of mouse mutants causes hypodontia and oligodontia. Hum Mol Genet 2005;14:3605-3617.
15. Vainio S, Karavanova I, Jowett A, Thesleff I. Identification of BMP-4 as a signal mediating secondary induction between epithelial and mesenchymal tissues during early tooth development. Cell 1993;75:45-58.
16. Turecková J, Sahlberg C, Aberg T, Ruch JV, Thesleff I, Peterkova R. Comparison of expression of the *msx1*, *msx-2*, *BMP-2* and *BMP-4* genes in the mouse upper diastemal and molar primordia. Int J Dev Biol 1995;39:459-468.
17. Kapadia H, Mues G, D'Souza R. Genes affecting tooth morphogenesis. Orthod Craniofac Res 2007;10:237-244.
18. Bei M, Chen Y, Woo I. The biological mechanisms of tooth eruption, resorption and replacement by implants. Boston: Harvard Society for the Advancement of Orthodontics 1996;431-440.
19. Chen Y, Bei M, Woo I, Satokata I, Maas R. *Msx-1* controls reciprocal inductive signaling in mammalian tooth morphogenesis. Development 1996;122:3033-3044.
20. Bei M, Maas R. FGFs and BMP4 induce both *Msx1*-independent and *Msx1*-dependent signaling pathways in early tooth development. Development 1998;125:4325-4333.
21. Liu W, Wang H, Zhao S, Zhao W, Bai S Zhao Y, Xu S, Wu C, Huang W, Chen Z, Feng G, He L. The novel gene locus for agenesis of permanent teeth (He-Zhao deficiency) maps to chromosome 10q11.2. J Dent Res 2001;80:1716-1720.
22. Thomas BL, Tucker AS, Qui M, Ferquson CA, Hardcastle Z, Rubenstein JL, Sharpe PT. Role of *Dlx-1* and *Dlx-2* genes in patterning of the murine dentition. Development 1997;124:4811-4818.
23. Nieminen P, Arte S, Pirinen S, Peltonen L, Thesleff I. Gene defect in hypodontia: exclusion of *MSX1* and *MSX2* as candidate genes. Hum Genet 1995;96:305-308.
24. Arte S, Nieminen P, Apajalahti S, Haavikko K, Thesleff I, Pirinen S. Characteristics of incisor-premolar hypodontia in families. J Dent Res 2001;80:1445-1450.
25. Arte S, Nieminen P, Pirinen S, Thesleff I, Peltonen L. Gene defect in hypodontia: exclusion of *EGF*, *EGFR* and *FGF-3* as candidate genes. J Dent Res 1996;75:1346-1352.
26. Itin PH, Fistarol SK. Ectodermal dysplasias. Am J Med Genet C Semin Med Genet 2004;131C:45-51.
27. Courtois G. The NF-kappaB signaling pathway in human genetic diseases. Cell Mol Life Sci 2005;62:1682-1691.
28. Headon DJ, Emmal SA, Ferguson BM, Tucher AS, Justice MJ, Sharpe, PT, Zonana J, Overbeek PA. Gene defect in ectodermal dysplasia implicates a death domain adapter in development. Nature 2001;414:913-916.
29. Döffinger R, Smahi A, Bessia C, Geissmann F, Feinberg J, Durandy A, Bodemer C, Kenwrick S, Dupuis-Girod S, Blanche S, Wood P, Rabia SH, Headon DJ, Overbeek PA, Le Deist F, Holland SM, Belani K, Kumararatne DS, Fischer A, Shapiro R, Conley ME, Reimund E, Kalhoff H, Abinun M, Munnich A, Israël A, Courtois G, Casanova JL. X-linked anhidrotic ectodermal dysplasia with immunodeficiency is caused by impaired NF-kappaB signaling. Nature Genet 2001;27:277-285.
30. Brunner HG, Hamel BC, Van Bokhoven H. The *p63* gene in EEC and other syndromes. J Med Genet 2002;39:377-381.
31. Strano S, Munarriz E, Rossi M, Castagnoli L, Shaul Y, Sacchi A, Oren M, Cesareni G, Blandino G. Physical interaction with Yes-associated protein enhances p73 transcriptional activity. J Biol Chem 2001;276:15164-15173.
32. Chi SW, Ayed A, Arrowsmith CH. Solution structure of a conserved C-terminal domain of p73 with structural homology to the SAM domain. EMBO J 1999;18:4438-4445.
33. Yang A, Schweitzer R, Sun D, Kaghad M, Walker N, Bronson RT, Tabin C, Sharpe A, Caput D, Crum C, McKeon F. p63 is essential for regenerative proliferation in limb, craniofacial and epithelial development. Nature 1999;398:714-718.
34. Kondo S, Schutte BC, Richardson RJ, Bjork BC, Knight AS, Watanabe Y, Howard E, de Lima RL, Daack-Hirsch S, Sander A, McDonald-McGinn DM, Zackai EH, Lammer EJ, Aylsworth AS, Ardinger HH, Lidral AC, Pober BR, Moreno L, Arcos-Burgos M, Valencia C, Houdayer C, Bahuau M, Moretti-Ferreira D, Richieri-Costa A, Dixon MJ, Murray JC. Mutations in *IRF6* cause Van der Woude and popliteal pterygium syndromes. Nature Genet 2002;32:285-289.
35. Sertié AL, Sousa AV, Steman S, Pavanello RC, Passos-Bueno MR. Linkage analysis in a large Brazilian family with van der Woude syndrome suggests the existence of a susceptibility locus for cleft palate at 17p11.2-11.1. Am J Hum Genet 1999;65:433-440.
36. Murray JC, Bennett SR, Kwitek AE, Small KW, Schinzel A, Alward WL, Weber JL, Bell GI, Buetow KH. Linkage of Rieger syndrome to the region of the epidermal growth factor gene on chromosome 4. Nat Genet 1992;2:46-49.
37. Phillips JC, del Bono EA, Haines JL, Pralea AM, Cohen JS,Freff LJ, Wiggs JL. A second locus for Rieger syndrome maps to chromosome 13q14. Am J Hum Genet 1996;59:613-619.
38. St Amand TR, Zhang Y, Semina EV, Zhao X, Hu Y, Nguyen L, Murray JC, Chen Y. Antagonistic signals between BMP4 and FGF8 define the expression of Pitx1 and Pitx2 in mouse tooth-forming anlage. Dev Biol 2000;217:323-332.
39. Lu MF, Pressman C, Dyer R, Johnson RL, Martin JF. Function of Rieger syndrome gene in left-right asymmetry and craniofacial development. Nature 1999;401:276-278.
40. Liu W, Dong X, Mai M, Seelan RS, Taniguchi K, Krishnadath KK, Halling KC, Cunningham JM, Boardman LA, Qian C, Christensen E, Schmidt SS, Roche PC, Smith DI, Thibodeau SN. Mutations in *AXIN2* cause colorectal cancer with defective mismatch repair by activating beta-catenin/TCF signalling. Nat Genet 2000;26:146-147.
41. Lammi L, Arte S, Somer M, Jarvinen H, Laherno P, Thesleff I, Pirinen S, Nieminen P. Mutations in *AXIN2* cause familial tooth agenesis and predispose to colorectal cancer. Am J Hum Genet 2004;74:1043-1050.