

Tooth Agenesis

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Advanced article

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Tooth agenesis denotes a condition where teeth are missing due to a developmental failure. According to severity, this malformation can be subdivided into hypodontia, oligodontia and anodontia. With a frequency of 20–30%, tooth agenesis is the most prevalent dental dysplasia, but not all teeth are equally affected. Familial occurrence and concordance in twins indicate potential genetic causes. Thus far, mutations could be identified for the genes *MSX1*, *PAX9* and *AXIN2*. All result in oligodontia. It is assumed that the defects cause haploinsufficiency, reducing the functional gene products below a critical level, which is required for normal odontogenesis. Both hypodontia and oligodontia can occur as an isolated dental malformation or in combination with defects in other organs, for example the skin and its appendages. Such syndromes can result from genetic defects affecting *MSX1* and the EDA signalling pathway. In the case of isolated hypodontia, associations have been found with sequence variants of several genes.

Introduction

The term tooth agenesis denotes a malformation characterised by the congenital absence of primary (deciduous) and/or permanent teeth, because they fail to develop. The term hypodontia is used ambiguously, either as a synonym for tooth agenesis or for milder forms of the condition, where up to six permanent (excluding the third molars) teeth are missing (Figure 1a). Agenesis of more than six teeth is referred to as oligodontia (Figure 1b), and the term anodontia is used when all teeth fail to develop, which occurs very rarely and only in some forms of ectodermal dysplasia (EDA). From both a biological and clinical point of view it is arguable, why missing permanent third molars commonly are disregarded and whether absence of all maxillary or mandibular teeth of a certain type, that is, incisors,

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canines, premolars and molars, should also be referred to as oligodontia, even if the number does not exceed six.

Irrespective of the severity, congenitally missing teeth pose medical problems challenging primarily dentists practicing in the fields of orthodontics and prosthetic dentistry, which have to decide whether spaces caused by the absence of teeth can be closed orthodontically or have to be bridged by prosthetic reconstructions. For biologists, cases of tooth agenesis can help to elucidate mechanisms involved in human odontogenesis, when phenotypes are carefully evaluated and correlated with associated genotypes. Phenotypes can be restricted to the dentition or include also defects in other tissues or organs, most frequently clefts of the lip and/or palate as well as defects of the skin and its appendages, that is, hairs, nails and glands. Some of these so-called syndromic forms of tooth agenesis were among the first cases for which causative mutations could be identified (Vastardis *et al.*, 1996; Kere *et al.*, 1996). However, during recent years many additional genetic defects responsible for failure of dental development have been elucidated, and even in cases of mild hypodontia, potential genetic causes have emerged.

Frequency and Characteristics of Tooth Agenesis

With an overall frequency amounting to 20–30% of individuals tooth agenesis is the most prevalent dental malformation. However, it does not equally affect both generations and all types of teeth, but rather reveals some characteristic patterns, which raise questions as to current concepts regarding the regulation of normal tooth development. Tooth agenesis is more frequent (1) in Europe and Australia than in North America, (2) in females than in males (Rølling and Poulsen, 2009), (3) in permanent than in primary teeth (prevalence <1%) (Ravn, 1971; Järvinen and Lehtinen, 1981), and (4) in the teeth of a type formed last compared to those formed first (Polder *et al.*, 2004). Thus, one or more permanent third molars, that is, wisdom teeth which are the last formed permanent molars, are congenitally missing in over 20% of the individuals, whereas the prevalences of agenesis of permanent mandibular second premolars, maxillary second premolars and maxillary lateral incisors are approximately 3%, 1.7% and 1.5%, respectively (Polder *et al.*, 2004). Conversely,

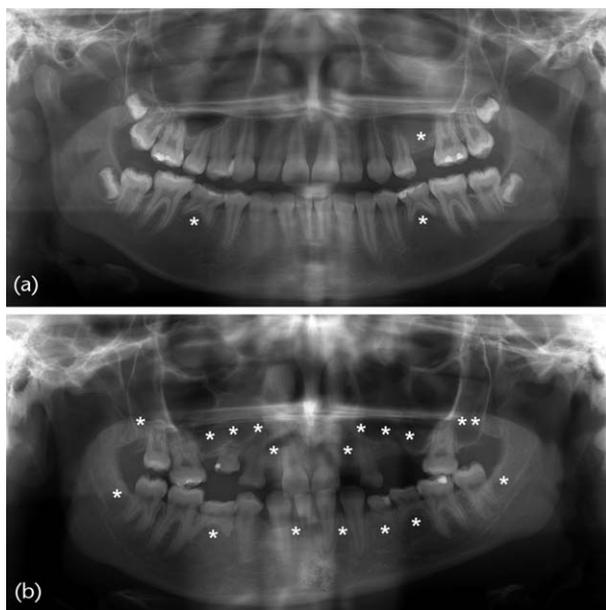


Figure 1 Panoramic radiographs of two examples of tooth agenesis. (a) Hypodontia with congenital absence of three of the four permanent second premolars; note the presence of all four permanent third molars. (b) Oligodontia with congenital absence of all four permanent third molars, second premolars, and lateral incisors; additional missing permanent teeth are the maxillary first premolars and canines, the left maxillary second molar, and the mandibular left first premolar.

permanent maxillary central incisors as well as maxillary and mandibular canines and first molars show the highest developmental stability among the human teeth. Even if hypodontia is nonsyndromic, it is associated with a significant reduction in the size of the teeth present (Brook *et al.*, 2002, 2009; Daugaard *et al.*, 2010). This observation has been interpreted to indicate that tooth agenesis may be an extreme form of tooth size reduction, which occurs below a certain critical level of odontogenic potential (Brook *et al.*, 2002). However, this threshold seems to vary considerably between the primary and permanent dentition as well as between the various permanent teeth.

Genetic Defects Responsible for Tooth Agensis

Nonsyndromic oligodontia is much less frequent than the milder hypodontia and occurs in only approximately 0.1–0.2% of individuals (Polder *et al.*, 2004). Nevertheless, causative mutations could thus far only be identified for these severe forms of tooth agenesis, which are inherited as autosomal dominant traits. Identified defects affect the *MSX1*, *PAX9* and *AXIN2* genes (Matalova *et al.*, 2008; Nieminen, 2009). *MSX1* and *PAX9* code for a homeobox and paired-box transcription factor, respectively, whereas the product of *AXIN2* is an intracellular antagonist of Wnt (wingless/integration) signalling (Nieminen, 2009). In mice

which exhibit stages of tooth formation (placode, bud, cap and bell) very similar to those seen in humans, *Msx1*, *Pax9* and Wnt signalling are important regulators of early dental development, controlling the transition from the placode to the bud as well as from the bud to the cap stage (De Coster *et al.*, 2009; Nieminen, 2009). Homozygous ablation of either of these genes causes craniofacial defects and results in anodontia due to a complete arrest of tooth development at the bud stage, whereas heterozygous null mutants do not show any phenotype. **See also:** [Mammalian Embryo: Wnt Signalling](#); [Pax Genes: Evolution and Function](#); [Signal Transduction Pathways in Development: Wnts and their Receptors](#); [Tooth Morphogenesis and Patterning: Molecular Genetics](#); [Transcription Factors and Human Disorders](#)

Based on the mutated deoxyribonucleic acid (DNA) sequences found in humans with tooth agenesis, it can be predicted that the consequences of the genetic defects are either severely truncated proteins or proteins with a deficient capacity to bind to DNA. Thus, in a heterozygous condition where one allele is mutated whereas the other allele is normal, the amount of the fully functional gene products is reduced approximately by half. This is assumed to lead to a haploinsufficiency and, thus, to a discontinuation of early odontogenesis similar to that observed in null mutant mice. Although the defects found in humans are less severe than in a knock-out, they obviously entail a reduction in functional gene product below a threshold required for normal dental development (Nieminen, 2009). However, contrary to expectations that reduced quantities of a gene product should equally affect the formation of all teeth, oligodontia caused by defects in *MSX1* and *PAX9* yields typical, although variable and overlapping patterns of tooth agenesis (Nieminen, 2009). Heterozygous disease-causing mutations of *MSX1* result in the absence of all permanent third molars, all second premolars, maxillary first premolars and variably other teeth (comparable to the case shown in **Figure 1b**), whereas defects in *PAX9* cause mainly agenesis of molars, typically of all permanent maxillary and the second and third mandibular molars as well as variably of other teeth. Based on the presumed role of Wnt signalling in dental development, the pathogenesis of oligodontia due to mutations in *AXIN2* is less clear. The phenotype of tooth agenesis seems to overlap with those resulting from defects of *MSX1* and *PAX9*, however data concerning *AXIN2* has been derived from only one family (Lammi *et al.*, 2004). Interestingly, none of the mutations identified so far in the three genes causing nonsyndromic oligodontia affected the permanent maxillary central incisors. Thus certain teeth, for example permanent third molars, second premolars and lateral incisors appear to be particularly susceptible and others such as primary teeth as well as permanent maxillary central incisors and canines seem to be particularly robust to reduced quantities of the functional gene products. An explanation for this observation does not seem to exist, obviously because some details of human tooth formation are not yet fully understood. **See also:** [Haploinsufficiency](#)

Both hypodontia and oligodontia can also occur as syndromic forms of tooth agenesis. Clefts of the lip and/or palate are often associated with hypodontia, notably not only in the cleft region, but also in more remote areas of the dentition (De Coster *et al.*, 2009; Nieminen, 2009). In van der Woude syndrome 1 (VWS1) which results from mutations of *IRF6* (interferon regulatory factor 6), hypodontia is combined with cleft lip/palate and pits of the lower lip (De Coster *et al.*, 2009). Another syndrome involving oral clefts and hypodontia is the velocardiofacial syndrome (VCFS), also referred to as DiGeorge syndrome or 22q11.2 deletion syndrome. Its cause is either an interstitial deletion of chromosomal region 22q11.21–q11.23 which encompasses the *TBX1* (T-box 1) gene or mutations of *TBX1*. Although the phenotype varies, it frequently includes clefts of the palate, cardiac malformations, velopharyngeal insufficiency and tooth agenesis affecting primarily the permanent second premolars, which are missing significantly more often than in the general population (Heliövaara *et al.*, 2011). Additional syndromes comprising congenital absence of only a few teeth are Axenfeld-Rieger syndrome type 1 and Sotos syndrome. Axenfeld-Rieger syndrome type 1 (in brief Rieger syndrome) is caused by mutations in *PITX2* (coding for the paired-like homeodomain transcription factor 2). Affected patients exhibit malformations of the eye and a peculiar phenotype of hypodontia, which usually involves also the otherwise rarely affected permanent maxillary central incisors (Wang *et al.*, 2003; Nieminen, 2009). Sotos syndrome results from mutations in the *NSD1* gene or microdeletions affecting the entire *NSD1* gene. It is characterised by abnormally tall stature and increased head dimensions primarily during childhood and adolescence as well as by facial dysmorphism. Similar to VCFS, hypodontia affects primarily permanent second premolars and less frequently third molars (Kotilainen *et al.*, 2009; Hirai *et al.*, 2011). Syndromal oligodontia combined with dysplasias of the finger and toe nails occurs in Witkop syndrome which is caused by defects of *MSX1*, which is a gene also involved in nonsyndromic tooth agenesis (Jumlongras *et al.*, 2001). The best-known syndromes comprising congenital absence and changes in shape of teeth combined with defects in skin appendages are the various forms of EDA. The hypohidrotic EDAs, which are inherited as X-linked as well as autosomal dominant or recessive traits, result from mutations in genes involved in the EDA signalling pathway, that is, *EDA* (coding for the signalling factor ectodysplasin A), *EDAR* (coding for the ectodysplasin A receptor), *EDAR-RAD* (coding for the signalling mediator EDAR-associated death domain), and *IKKKG* (also referred to as *IKK γ* or *NEMO*, coding for the NEMO protein, that is, another signalling mediator) (De Coster *et al.*, 2009; Nieminen, 2009). Based on findings from experiments in mice it is assumed that EDA signalling is important for the proper formation of the dental placode and the so-called enamel knot, which arises at the cap stage. This dual effect could account for the observed combination of tooth agenesis and changes in shape of teeth present, which is a typical

feature of EDA. Remarkably, tooth agenesis resulting from defective EDA signalling in humans also affects the primary dentition, possibly as a result of the early disruption of placode formation (Nieminen, 2009). **See also:** Craniofacial Defects and Cleft Lip and Palate; Dental Anomalies: Genetics; Transcription Factors and Human Disorders

The observation that agenesis of only a few teeth exhibits significant familial occurrence and frequent concordance in twins, suggests a genetic contribution to these mild forms of hypodontia as well. If the assumption is correct that a reduction of the odontogenic potential below a critical level leads to failure of tooth development, it can be speculated that DNA sequence variants (polymorphisms), which entail only a mild deficiency of the respective gene products result in agenesis of only a few, particularly susceptible teeth. Consequently, genes found to be associated with isolated and syndromic oligodontia have also been examined in cases of hypodontia. As far as *MSX1* and *PAX9* are concerned, the results of these searches were inconsistent (Scarel *et al.*, 2000; Vieira *et al.*, 2004; Pan *et al.*, 2008; Pinho *et al.*, 2010; Paixão-Cortes *et al.*, 2011). However, significant associations of tooth agenesis and variants and haplotypes were found with respect to *TGFA* (the gene for transforming growth factor- α) (Vieira *et al.*, 2004; Callahan *et al.*, 2009a), *IRF6*, *FGFR1* (fibroblast growth factor receptor 1) (Vieira *et al.*, 2007, 2008), *MMP1*, *MMP20* (matrix metalloproteinases 1 and 20) (Küchler *et al.*, 2011), *AXIN2* (Callahan *et al.*, 2009b) and *EDA* (Mues *et al.*, 2009). Thus there does not seem to be a major locus accounting for hypodontia. **See also:** Dental Anomalies: Genetics

Conclusions

Severe forms of isolated tooth agenesis, that is oligodontia, result from mutations in the *MSX1*, *PAX9* and *AXIN2* genes. Mild forms of hypodontia appear to be associated with variants of additional genes. It is assumed that a reduction below a critical threshold in the quantity of a gene product essential for early dental development leads to tooth agenesis. However, this assumption neither accounts for the observed typical patterns of oligodontia nor does it explain, why certain teeth are more susceptible to agenesis than others.

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Further Reading

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Web Links

- Gene Expression in Tooth <http://bite-it.helsinki.fi>
- Online Mendelian Inheritance in Man (OMIM) <http://www.ncbi.nlm.nih.gov/Omim>
- Entries: 119300 (van der Woude syndrome), 192430 (velocardiofacial syndrome), 180500 (Axenfeld-Rieger syndrome type 1), 117550 (Sotos syndrome), 189500 (Witkop syndrome), 305100, 300291, 224900 (ectodermal dysplasia), 142983 (*MSX1*), 167416 (*PAX9*), 604025 (*AXIN2*), 607199 (*IRF6*), 602054 (*TBX1*), 601542 (*PITX2*), 606681 (*NSD1*) 300451 (*EDA*), 604095 (*EDAR*), 606603 (*EDARRAD*), 300248 (*IKBKG*), 190170 (*TGFA*), 136350 (*FGFR1*), 120353 (*MMP1*), 604629 (*MMP20*)