IN BRIEF

Provides general dental practitioners with:
- Current knowledge on the aetiological basis of human hypodontia.
- Clinical features and classification of this common dental anomaly.
- A summary of the syndromic forms of this condition.

Familial human hypodontia – is it all in the genes?

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The congenital absence of teeth is one of the commonest developmental abnormalities seen in human populations. Familial hypodontia or oligodontia represents an absence of varying numbers of primary and/or secondary teeth as an isolated trait. While much progress has been made in understanding the developmental basis of tooth formation, knowledge of the aetiological basis of inherited tooth loss remains poor. The study of mouse genetics has uncovered a large number of candidate genes for this condition, but mutations in only three have been identified in human pedigrees with familial hypodontia or oligodontia: *MSX1*, *PAX9* and *AXIN2*. This suggests that these conditions may represent a more complex multifactorial trait, influenced by a combination of gene function, environmental interaction and developmental timing. Completion of the human genome project has made available the DNA sequence of the collected human chromosomes, allowing the localisation of all human genes and, ultimately, determination of their function. Therefore it is likely that our understanding of this complex developmental process will continue to improve, not only during normal development but also when things go wrong.

INTRODUCTION

There can be few dental surgeons who have not pondered the mysteries surrounding congenital tooth absence at some point in their career. A genetic basis for the embryonic mechanisms underlying tooth formation is clear, even at an anecdotal level. A wide variety of animals have highly adapted and species-specific dentitions; in human populations defects of tooth development often affect particular teeth and these anomalies frequently run in families, while defects in tooth number are often associated with other anomalies of dental development (Table 1). The genetic mechanisms responsible for generating such a regionally diverse but homologous structure as the mature human dentition are still poorly understood, but progress has been made over the last decade, largely with the use of mouse models.[1-3] In recent years, homologues of some candidate mouse genes have been identified as having a role in human dental development, particularly in the aetiology of congenitally absent teeth.[4,5] However, given the large number of candidates and the prevalence of this condition, it is surprising that more genes have not been identified to date.

Clinical genetics

Hypodontia is often used as a collective term for congenitally missing teeth, although specifically it describes the absence of one to six teeth, excluding third molars (Table 2). Oligodontia refers to the absence of more than six teeth, excluding third molars, while anodontia represents a complete failure of one or both dentitions to develop.[6] Hypodontia can either occur with accompanying genetic disease as part of a recognised clinical syndrome, or as a non-syndromic, familial form, which occurs as an isolated trait, affects variable numbers of teeth and appears either sporadically or in a familial fashion within a family pedigree[7] (Fig. 1).

Online Mendelian Inheritance in Man (OMIM) lists over 60 different syndromic conditions that include hypodontia as part of their phenotypic spectrum of anomalies[8] and candidate genes have been identified for many of these conditions (Table 3). However, possibly of more relevance to the general dental practitioner is the more common non-syndromic or familial form of hypodontia (Fig. 1). This condition can follow autosomal dominant,[9-12] autosomal recessive[13,14] or sex-linked[15] patterns of inheritance, with considerable variation in both penetrance and expressivity. Indeed, a multifactorial model has been suggested to explain the inheritance of anomalies in both tooth number and size with the phenotypic effect being related to

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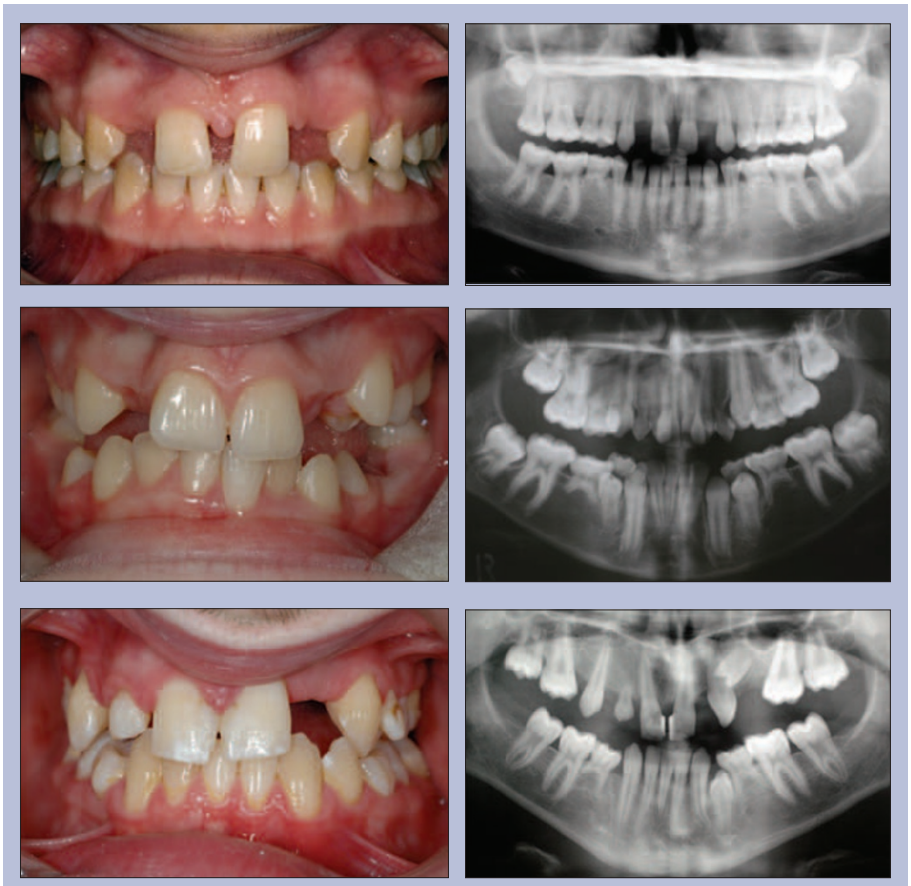

Fig. 1 Non-syndromic hypodontia and oligodontia
In the upper panel there is hypodontia with UR2, UL2, LL8, LL5, LR5 and LR8 absent. In the middle panel there is more severe hypodontia, with UR8, UR5, UR4, UL4, UL5, UL8, LR8, LR5, LL5 and LL8 absent. In the lower panel there is oligodontia, with the UR8, UR5, UR4, UR2, UL2, UL5, UL8, LL8, LL5, LL1, LR4, LR5, LR8 absent

certain thresholds, themselves influenced by both genetic and environmental factors.[16,17] Clearly, within this model, the mutation of a major gene may be a significant enough event to result in inherited tooth loss.

It is important for the general dental practitioner to fully assess any patient presenting with hypodontia and referral to a specialist clinic is often desirable. In some cases this condition can be indicative of underlying genetic disease and further referral for genetic testing might be desirable. Treatment of this condition aims to improve both aesthetics and function, and is often facilitated through a multidisciplinary approach.[18,19]

Non-syndromic hypodontia

Non-syndromic hypodontia is by far the most common form of congenital tooth absence and can involve variable numbers of teeth. It is more commonly seen in the secondary dentition, but in the rare cases of missing primary teeth that do occur, there is often a strong tendency towards further tooth absence in the secondary teeth. Anodontia (OMIM #206780) represents the most severe form of non-syndromic hypodontia, but is extremely rare in the absence of accompanying genetic disease,[20] while oligodontia (OMIM #604625) is only seen at a level of around 0.25% within European populations.[21,22] The more localised incisor-premolar type of hypodontia affects only one or a few teeth (OMIM #106600), but occurs more commonly in around 8% of the population.[7] Within these clinical entities, certain teeth fail to develop more often than others. Third molars are the most commonly absent tooth in the dentition, with at least one being absent in anything up to 20-30% of the population. This is followed in Europeans by the mandibular second premolar, maxillary lateral incisor and premolars (around 2%) and the mandibular central incisor (0.2%).[23] The absence of canine teeth, first molars and second molars is extremely rare in hypodontia;[24] if these teeth are missing, it is usually seen in association with severe forms of syndromic oligodontia.

Candidate genes

If genes are so important in controlling tooth development, what do we know about potential candidates within the human genome? As with many aspects of mammalian development, the mouse has become one of the principle model organisms for the study of these embryonic processes and a host of genes, encoding members of numerous protein families, are expressed during development of the mouse tooth.[1,3,25] Targeted deletion in many such genes within knockout mice can disrupt tooth formation. These data have provided a reference point in the search for candidate genes that may play a role in the aetiology of human forms of hypodontia.[26] In particular, two genes that encode members of transcription factor families have attracted considerable attention because of their role in murine tooth development.

Msx1 (Muscle segment homeobox) is a member of a distinct sub-family of homeobox genes, which is expressed in spatially restricted regions of the head during early development, localising to regions of condensing embryonic connective tissue or ectomesenchyme in the tooth germ[27,28] (Fig. 2). Furthermore, analysis of mice lacking a functional *Msx1* gene reveals that all tooth development arrests at the bud stage.[29] These findings demonstrate that in the mouse at least, *Msx1* is essential for normal odontogenesis. *Pax9* encodes a member of another transcription factor protein family, characterised by the presence of a DNA-binding paired-box domain. In the mouse embryo, *Pax9* is also expressed in the prospective mesenchymal compartment of developing teeth[30] (Fig. 2) and is essential during later stages of tooth development; mice with targeted mutations in *Pax9* also exhibit tooth arrest at the bud stage.[31] These two genes are therefore excellent candidates for human forms of hypodontia and have been the subject of intense scrutiny within human pedigrees affected by non-syndromic tooth loss.

MSX1

Consistent with the mouse phenotype, mutations in the human *MSX1* gene have been associated with familial oligodontia[12,32] and certain forms of syndromic hypodontia;[33,34] however, associations with the more common incisor-premolar form of familial hypodontia are less

common.[7,35] The relationship of *MSX1* to familial incisor-premolar hypodontia was originally investigated in five Finnish families, with a total of 20 affected individuals; but no linkage was identified.[7] However, these findings did not rule out a defect in *MSX1* being associated with other forms of hypodontia and analysis of a family affected with oligodontia identified a causative locus on chromosome 4p where the *MSX1* gene resides.[12] Sequence analysis demonstrated a missense mutation within a critical region of the MSX1 protein in all affected family members. This protein was subsequently found to be inactive *in vivo* and haploinsufficiency concluded to be the probable cause of the phenotype.[36] A frameshift mutation in *MSX1* has been identified in a family demonstrating non-syndromic hypodontia with absence of all second premolars and mandibular central incisors.[37] Further studies have also demonstrated a role for *MSX1* in the aetiology of some forms of syndromic hypodontia. A Dutch family showing various combinations of cleft lip, cleft palate and tooth agenesis were identified with a nonsense mutation in exon 1[33] and a further nonsense mutation has been shown to be responsible for Witkop syndrome (OMIM #189500), an autosomal dominant form of ectodermal dysplasia involving nail dysplasia and variable numbers of congenitally missing permanent and/or primary teeth.[34]

PAX9

A number of mutations[38-43] and polymorphisms in the upstream promoter region[44] of the human *PAX9* gene have been identified in association with variable forms of oligodontia, that particularly affect the molar dentition. A family exhibiting hypodontia of most permanent molars and variable absence of second premolars and mandibular incisors were originally identified with a single base insertion that produced a frameshift mutation and premature termination of the PAX9 protein.[38] Significantly, this mutation alters the amino acid sequence within the highly conserved (paired box) region of the gene, producing reduced DNA binding of the mutant protein.[45] However, another frame-shift insertional mutation outside this region can also produce hypodontia.[40] Further single basepair mutations in *PAX9* have since been identified in association with molar hypodontia, including nonsense[39] and missense;[41] in addition to a large 288 basepair insertion.[41] Interestingly, while molar tooth development does seem to be particularly sensitive to alterations in PAX9 function, a *PAX9* mutation has also been associated with a non-familial form of oligodontia affecting third molars, premolars and some incisor teeth.[42] Haploinsufficiency of *PAX9* seems to be the underlying cause of the hypodontia in these affected pedigrees, a finding reinforced by the identification of a rare father and daughter kindred affected by complete primary and permanent molar hypodontia with a deletion of one copy of their *PAX9* gene.[46]

MSX1 and PAX9?

In addition to mutational analysis and the identification of candidate genes, biologists are now attempting to understand some of the molecular interactions underlying tooth development failure. There is now evidence to suggest that PAX9 and MSX1 interact during odontogenesis at both the gene and protein levels. Clues to this relationship are present in mice; expression of these genes co-localise in the developing tooth (Fig. 2), odontogenesis arrests at the bud stage in both mouse knockouts[29,31] and this phenotype is also accompanied by a marked reduction in expression of the gene encoding Bone morphogenetic protein 4 (*Bmp4*) in both mouse lines. *Bmp4* encodes a signalling molecule with a key role during transition of the tooth germ from bud to cap stage.[28,47] Initial evidence of an interaction in humans came from a genetic epidemiological study[48] and has since been confirmed by biochemical analyses; mammalian Pax9 is able to form a physical association with Msx1.[49] This interaction takes the form of a heterodimeric protein complex, which enhances the ability of Pax9 to activate both *Msx1* and *Bmp4* gene expression during tooth development. Importantly, simulation of a known *Pax9* mutation has also been shown to lack the ability to activate transcription of these target genes, even though a physical interaction with Msx1 still occurs.[49]

AXIN2

The identification of a four-generation Finnish family affected by autosomal dominant oligodontia has recently provided a rather unexpected further insight into the genetics of inherited tooth loss. Within this family, 11 members were identified as lacking at least eight permanent teeth and rather surprisingly, further investigation of this pedigree suggested that among these individuals affected by oligodontia, a significant risk of developing colorectal neoplasia was also present.[50] Linkage analysis of this pedigree identified a candidate region on chromosome 17, which contained approximately 80 genes, among which

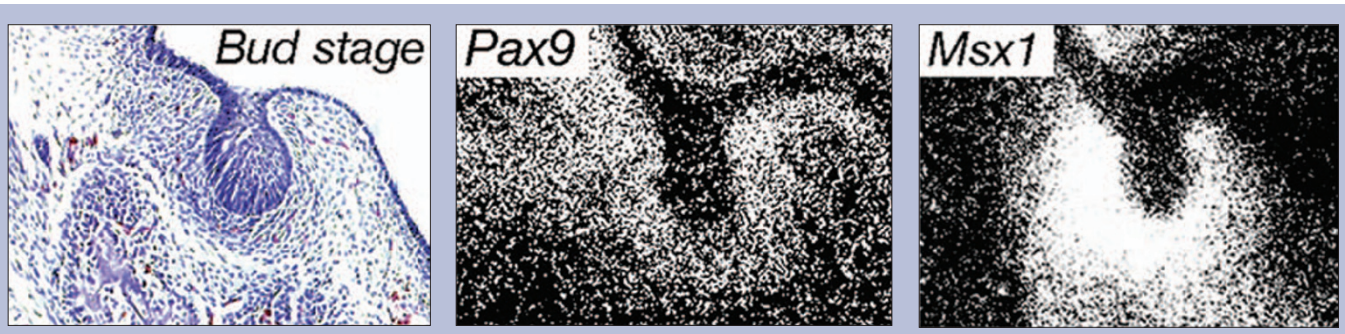

Fig. 2 Expression of *Pax9* and *Msx1* in the developing tooth
At the bud stage of dental development both *Pax9* and *Msx1* are expressed in the ectomesenchymal component of the tooth germ, the dental papilla and follicle. These corresponding expression domains are consistent with biochemical evidence of interaction between these two proteins in the developing tooth

Table 1 Dental anomalies seen in association with hypodontia

Reduced crown and root size
Conical crown shape
Enamel hypoplasia
Molar taurodontism
Delayed eruption
Prolonged retention of primary teeth
Infraocclusion of primary teeth
Tooth impaction, particularly maxillary canines
Ectopic eruption
Transposition
Lack of alveolar bone
Reduced vertical dimensions
Increased overbite

Table 2 Classification of inherited tooth loss

Non-syndromic (familial)	Hypodontia
	Oligodontia
	Anodontia
Syndromic	Hypodontia
	Oligodontia
	Anodontia

Table 3 Syndromic conditions associated with hypodontia

OMIM	Syndrome	Gene	Protein product
#190685	Down syndrome	*Trisomy* 21	
#305100	Anhidrotic ectodermal dysplasia *	*EDA*[58]	Proteinase
#103285	ADULT syndrome †	*TP63*[59]	Tumour protein
#603543	Limb mammary syndrome (LMS) †	*TP63*[60]	Tumour protein
#225410	Ehlers Danlos (Type VII) syndrome	*ADAMTS2*[61]	Proteinase
#308300	Incontinentia pigmenti	*NEMO*[62]	Transcription factor activator
#180500	Rieger syndrome (Type 1)	*PITX2*[63]	Transcription factor
#189500	Witkop syndrome	*MSX1*[34]	Transcription factor

(*) There are more than 150 clinically distinct hereditary syndromes in which ectodermal dysplasia is present. Most syndromes are very rare and manifest variable defects in morphogenesis of ectodermal structures including hair, skin, nails, and teeth. In the X-linked recessive form (OMIM #305100) listed here, males are usually more severely affected and females show variable severity ranging from mild to severe. There are also autosomal recessive (OMIM #224900) and autosomal dominant (OMIM #129490) forms of the disorder. A distinct form of X-linked hypohidrotic ectodermal dysplasia with immune deficiency (OMIM #300291) has also been described. (†) In addition, a number of ectodermal dysplasia and clefting-type syndromes also exist, which demonstrate a mixed clefting phenotype in conjunction with the features of ectodermal dysplasia. A number of these are allelic disorders due to mutations in the TP63 gene, which include Acro-dermato-ungual-lacrimal-tooth syndrome (ADULT), Limb mammary syndrome (LMS), Ankyloblepharon-ectodermal dysplasia-cleft syndrome (AEC) (OMIM #106260), Ectrodactyly-ectodermal dysplasia-cleft lip/palate (EEC3) (OMIM #604292) and Rapp-Hodgkin syndrome (OMIM #129400). The issue is further complicated by the fact that TP63 is part of a three-member homologous family: TP53, TP63 and TP73.

was a gene called *AXIN2* (Axis inhibition protein-2). *AXIN2* was selected as a strong candidate gene for this condition for several reasons: its position within this particular chromosomal region, a previously identified association with colorectal carcinoma and the fact that AXIN2 is also a known regulator of the Wnt signalling pathway. The Wnt family of secreted proteins form part of a large family of signalling molecules that have a wide-ranging role during embryonic development and demonstrate regionally restricted expression in the tooth.[51] Suppression of Wnt signal transduction in mutant mice or over-expression in wild type jaw explants can inhibit tooth development.[52,53] Crucially, when further sequence analysis was carried out, all the affected family members within this pedigree had a nucleotide transition within exon 7 of *AXIN2*, which produced a nonsense mutation and premature termination of the encoded protein.[50] Several novel polymorphisms or variants of *AXIN2* have since been identified, which when present, also carry an increased risk of tooth agenesis to the individual.[54]

CONCLUSIONS

Given the large number of candidate genes that have been provided from studies in the mouse,[25] it is perhaps surprising that mutations in so few have been identified in human family pedigrees affected by hypodontia.[26] This suggests that in many cases, familial human hypodontia may represent a more complex, multifactorial condition. A number of subtle traits are apparent within human pedigrees possessing identifiable gene mutations in association with hypodontia. *MSX1* function is predominantly associated with premolar and occasionally molar agenesis, while *PAX9* mutations are almost always associated with missing molar and only occasionally premolar teeth. In contrast, hypodontia associated with *AXIN2* mutations involves a wider range of tooth types. These observations suggest that the combined and overlapping expression domains of genes expressed within the tooth-forming regions are important for normal development of the dentition, a finding consistent with observations in the mouse.[55,56] This threshold model is useful in explaining the lack of phenotypic penetrance and variability found in many pedigrees affected by hypodontia. However, it also provides some explanation for the observations that teeth along the margins of each field are more commonly absent (lateral incisors, second premolars, third molars).[57] It is the peripheral domains of gene expression that are most important in delineating tooth class, but also the most susceptible to perturbations in function.

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Appendix 1 Glossary of terms

Allelic disorders	Different disorders due to mutations in a single gene
Autosomal dominant	An autosomal dominant gene is one that occurs on an autosomal (non-sex determining) chromosome; as it is dominant, the phenotype it gives will be expressed even if the gene is heterozygous.

A further note explaining the terminology used in this article is helpful. Gene names are italicised, while proteins are not. Mouse genes and proteins are referred to in lower case while human are upper case.

Appendix 1 Glossary of terms	
Continued from page 207	
Autosomal recessive	An autosomal recessive gene is also one that occurs on an autosomal chromosome; recessive genes need to be homozygous to be expressed.
Bone morphogenetic proteins (BMPs)	A large group of signalling peptides within the transforming growth factor-β superfamily of signalling proteins
Frameshift mutation	A mutation that disrupts the normal translational reading frame of mRNA by adding or deleting a number of bases that are not a multiple of three
Genetic linkage analysis	A method to isolate disease genes based upon the fact that identifiable regions on chromosomes can be close enough to the gene of interest for them to remain associated after meiosis within affected families
Haploinsufficiency	A situation where 50% of the normal level of gene expression (ie in the heterozygous state) is not sufficient to support normal function
Heterodimer	A two-unit molecule where each unit is different
Homeobox	A highly conserved DNA sequence found within all homeobox genes that encodes a DNA binding homeodomain within the transcription factor, it is this homeodomain that physically interacts with the DNA of target genes
Homeobox genes	A large multi-family group of genes that encode transcription factors which act as important regulators of the transcription of other genes in the nuclei of target cells
Knockout mouse	A mouse genetically engineered to lack the function of both copies of a particular gene
Missense mutation	A type of mutation that produces a single amino acid change in the translated gene product
Nonsense mutation	A type of mutation that results in premature termination or elongation of the translated protein product of a particular gene
Polymorphism	The existence of two or more genetic variations at significant frequencies within the population, this can include sequence variations (usually at >1%)
Promoter region	A DNA sequence involved in initiating gene transcription
Sex linked	Sex linkage is the phenotypic expression of an allele that is related to the gender of the individual and is directly tied to the sex chromosomes; this mode of inheritance is in contrast to the inheritance of traits on autosomal chromosomes, where both sexes have the same probability of expressing the trait.
Signalling molecules	Proteins produced by a cell that bind to receptors on the surface of a particular target cell, the resulting activation of the signal transduction pathway leads to downstream gene transcription and ultimately changes of target cell fate
Transcription factors	Regulatory proteins that initiate or modify the transcription of a gene into RNA
A further note explaining the terminology used in this article is helpful. Gene names are italicised, while proteins are not. Mouse genes and proteins are referred to in lower case while human are upper case.	