Part 1

Background

1 Definitions, Prevalence and Aetiology

Introduction

Disturbances during the early stages of tooth formation may result in the developmental or congenital absence of one or more teeth. This condition has been described in the literature using a range of terms that can be a source of confusion since they are frequently neither synonymous nor mutually exclusive, and no single name is universally accepted.

The most widely employed general term is *hypodontia*, used by many to describe the whole spectrum of the disorder from the absence of a single tooth to the rare absence of all teeth (termed *anodontia*). Absent third permanent molars are generally not considered when assessing the presence and severity of hypodontia. To assist in diagnostic classification, the degree of severity of hypodontia has been arbitrarily described as:

- Mild: 1–2 missing teeth
- Moderate: 3–5 missing teeth
- Severe: 6 or more missing teeth

(From Goodman *et al.*, 1994; Dhanrajani, 2002; Nunn *et al.*, 2003; Jones, 2009).

In contrast, some authors have suggested that the term *hypodontia* should be employed solely to describe the absence of a few teeth, preferring the term *oligodontia* to describe the absence of a larger number of teeth (Nunn *et al.*, 2003). This has been further refined with the suggestion that the absence of one to six teeth should be termed *hypodontia*, while the absence of more than six teeth should be termed *oligodontia* (Arte and Pirinen, 2004; Polder *et al.*, 2004). Others have proposed that the term *oligodontia* should be further limited to describe the absence of six or more teeth with associated systemic manifestations, as seen in several syndromes (Goodman *et al.*, 1994; Nunn *et al.*, 2003). To reflect the differences in terminology, a further subdivision of hypodontia and oligodontia has been proposed into *isolated hypodontia/oligodontia* (non-syndromic) and *syndromic hypodontia/oligodontia* (associated with syndromes) (Schalk van der Weide *et al.*, 1992; Arte and Pirinen, 2004).

Current terminology also demonstrates geographical variations. The term *oligodontia* is often preferred in Europe, whereas the descriptive terms *agenesis* or *multiple dental agenesis* are often used in the USA. One historic and self-contradictory descriptor, which was once widely used but is now

Table 1.1   Terms used to describe the developmental or congenital absence of teeth.

Term	Definition	Common usage	Used in this book
Hypodontia	A developmental or congenital condition characterised by fewer than normal teeth	As defined Often sub-divided into mild (fewer than six teeth missing) and severe (six or more missing) forms*	A developmental or congenital condition characterised by fewer than normal teeth
Severe hypodontia	A developmental or congenital condition characterised by absence of six or more teeth	As defined Often used synonymously with oligodontia	A developmental or congenital condition characterised by absence of six or more teeth*
Oligodontia	A developmental or congenital condition characterised by fewer than normal teeth	As defined Often used synonymously with severe hypodontia	A developmental or congenital condition characterised by fewer than normal teeth in the presence of systemic manifestations
Anodontia	A developmental or congenital condition characterised by absence of all teeth	Sometimes sub-divided into anodontia and partial anodontia (now obsolete, but equates to hypodontia or oligodontia)	A developmental or congenital condition characterised by absence of all teeth

*By convention, third molars are excluded from the definition.

considered largely obsolete (and deprecated), is *partial anodontia* (Jones, 2009).

In this book we use the terms *hypodontia*, *oligodontia* and *anodontia* (Table 1.1). They are simple to employ and provide convenient labels for the relevant conditions, being of particular value in epidemiological studies. They are, however, defined solely by the number of missing teeth and take no account of the patterns of dental agenesis. In addition they do not include frequently encountered clinical features of hypodontia such as variations in the form and size of the teeth, delayed eruption, connective tissue changes, malpositioning of teeth, and occlusal disharmony, which means they are of limited value when assessing treatment needs.

Hypodontia is one factor in the clinical indices used by orthodontists when prioritising treatment, so reflecting the clinical importance of the condition for the patient concerned. The Index of Orthodontic Treatment Need (Dental Health Component) uses a five-point scale in which Category 5 indicates the greatest need for treatment (Shaw *et al.*, 1991; Waring and Jones, 2003; Ferguson, 2006). The absence of more than a single tooth in any one quadrant is assigned to Category 5, while cases in which there are fewer missing teeth are assigned to Category 4. These categories are based on a need for multidisciplinary care for more severe hypodontia, with the possibility of closure of spaces in milder cases. Other indices have also considered hypodontia as a factor with a high impact on dental status (Otuyemi and Jones, 1995; Shelton *et al.*, 2008).

Many societies now place considerably greater emphasis on oral health than they have done in the past. As a result, individuals with hypodontia are increasingly requesting treatment for their condition. It can be complex and expensive, particularly where advanced restorative care results in the need for lifetime dental maintenance (Forgie *et al.*, 2005; Thind *et al.*, 2005; Hobkirk *et al.*, 2006). It also often involves a number of specialist services, and consequently data on the prevalence of hypodontia within a given population are important for planning and allocating healthcare resources both at regional and national levels. Knowledge of the prevalence of hypodontia is also important when counselling patients and their carers (Lucas, 2000; Gill *et al.*, 2008).

Prevalence

Primary dentition

In the primary dentition, hypodontia is relatively uncommon. The prevalence of 0.1–0.9% is equally

distributed between males and females (Grahnen and Granath, 1961; Järvinen and Lehtinen, 1981; Carvalho et al., 1998; Dhanrajani, 2002; Nunn et al., 2003). It is most common in the anterior maxilla, with the lateral incisors being most frequently affected (Daugaard-Jensen et al., 1997). Hypodontia in the primary dentition is often associated with hypodontia in the permanent dentition (Whittington and Durward, 1996; Daugaard-Jensen et al., 1997; Arte and Pirinen, 2004), and can be used in the early counselling of affected individuals and their carers. In mild cases, hypodontia of the primary dentition often goes unnoticed or may be wrongly dismissed as of some interest but seemingly unimportant. Diagnosis in a younger patient is frequently made by general dental practitioners, who should have knowledge of the condition and be prepared to refer the patient early for specialist investigation and family counselling (Hobson et al., 2003; Gill et al., 2008).

Permanent dentition

Studies into the prevalence of hypodontia in the permanent dentition have frequently suffered from relatively small sample sizes (Polder et al., 2004) which is probably one of the reasons why reported prevalence often varies, even within similar populations, with ranges as wide as 0.3–36.5%. Although data on missing teeth are only available for a small number of racial groups (and inevitably some have been studied more thoroughly than others), it has been shown that the prevalence of hypodontia in females is higher in Europe and Australia than in North America (Flores-Mir, 2005). The same difference was also noted for males (Polder et al., 2004). The most extensive studies have been of Caucasian people, with a reported prevalence of hypodontia in the range 4.0–6.0% and among whom females are more frequently affected than males in the ratio of 3:2 (Egermark-Eriksson and Lind, 1971; Dhanrajani, 2002; Nunn et al., 2003; Larmour et al., 2005). In contrast, the prevalence of severe hypodontia, defined as the developmental absence of six or more teeth, has been reported at 0.14–0.3% in Caucasian people (Hobkirk and Brook, 1980; Polder et al., 2004).

In order to increase the sample size and thus improve the reliability of population data, Polder et al. (2004) conducted a meta-analysis which has added significantly to our knowledge. It included data from 33 studies, with a total sample size of approximately 127,000 individuals, and concluded that the prevalence of hypodontia in the permanent dentition varied between continents, racial groups and genders.

The reported prevalence in the population for different racial groups included white Europeans (4.6–6.3%), white North Americans (3.2–4.6%), black African–Americans (3.2–4.6%), white Australians (5.5–7.6%), Arabs (2.2–2.7%) and Chinese people (6.1–7.7%) (Polder et al., 2004). Other studies have examined the prevalence among white Scandinavians (4.5–6.3%) and Japanese people (7.5–9.3%) (Niswander and Sujaku, 1963; Endo et al., 2006a, 2006b). The data analysed confirmed that hypodontia was more prevalent in females than males (1.37:1), which closely approximates to the previously cited ratio of 3:2 found in smaller studies. Table 1.2 summarises the prevalence data in relation to ethnicity.

Table 1.2 Prevalence of dental agenesis by gender in different ethnic groups and male to female ratios in each ethnic group.

Ethnic group	Mean % males (CI)	Mean % females (CI)	Male to female ratio
European (white)	4.6% (4.5, 4.8)	6.3% (6.1, 6.5)	1:1.4
North American (white)	3.2% (2.9, 3.5)	4.6% (4.2, 4.9)	1:1.4
North American (African-American)	3.2% (2.2, 4.1)	4.6% (3.5, 5.8)	1:1.4
Australian (white)	5.5% (4.4, 6.6)	7.6% (6.0, 9.2)	1:1.4
Saudi Arabian (white)	2.7% (2.0, 3.4)	2.2% (1.2, 3.1)	1:0.8
Chinese (Mongoloid)	6.1% (4.0, 8.1)	7.7% (5.4, 10.0)	1:1.3

CI, confidence intervals. Data from Polder et al. (2004).

The reported sites and frequency of missing teeth both vary between studies. To evaluate the prevalence of absence of an individual tooth within a normal population, Polder *et al.* (2004) carried out a meta-analysis. This considered 10 studies with an aggregate sample of over 48,000 people. The frequency of absent teeth in *descending* order was:

- Mandibular second premolar (3.0%)
- Maxillary lateral incisor (1.7%)
- Maxillary second premolar (1.5%)
- Mandibular central incisor (0.3%)
- Mandibular lateral incisor and maxillary first premolar (0.2%)
- Mandibular first premolar (0.15%)
- Mandibular second molar and maxillary canine (0.1%)
- Maxillary second molar (0.05%)
- Maxillary first molar (0.03%)
- Mandibular canine (0.02%)
- Mandibular first molar (0.01%)
- Maxillary central incisor (0.005%)

This supports one of the widely accepted sequences of missing teeth as:

- Mandibular second premolar >
- Maxillary lateral incisor >
- Maxillary second premolar >
- Mandibular incisors

To consider the frequency of missing teeth within a sample of hypodontia patients, a meta-analysis examined data from 24 studies reporting on individuals with hypodontia with a total of approximately 11,500 absent teeth (Polder *et al.*, 2004). The absence of individual teeth within the hypodontia group had the same sequence as that described above, namely: mandibular second premolar (41.0%) > maxillary lateral incisor (22.9%) > maxillary second premolar (21.2%) > mandibular central incisor (3.5%) > maxillary first premolar (2.8%) > mandibular lateral incisor (2.5%). The remaining teeth were within the range 0.2–1.4%, supporting a previously expressed view that the absence of maxillary central incisors, canines and first molars is rare and principally occurs in patients with severe hypodontia, where there is the concomitant absence of the most frequently missing teeth (Hobkirk and Brook, 1980; Rózsa *et al.*, 2009).

Table 1.3 summarises data relating to the frequency of absent teeth within a group of hypodontia patients.

The majority of patients with developmentally missing teeth (83%) had only one or two teeth missing. Patients with three to five teeth missing represented 14.4% of the group, while severe hypodontia with six or more absent teeth was present in 2.6% of the sample. This was equated to a population prevalence of 0.14%.

The bilateral absence of a particular tooth in one jaw has been reported to be 54% for maxillary lateral incisors. These are the only teeth with a prevalence that is greater than 50% (with values of 49.25% for maxillary second premolars, 45.6% for mandibular second premolars and 41.2% for mandibular central incisors), hence it can be concluded that it is more common for maxillary lateral incisors to be absent bilaterally and other teeth to be absent unilaterally. Table 1.4 summarises data relating to the frequency of bilaterally absent teeth.

Table 1.3 Distribution of individual missing teeth for each jaw in patients with hypodontia.

Tooth	Maxilla	Mandible
I1	0.2%	3.5%
I2	22.9%	2.5%
C	1.3%	0.3%
P1	2.8%	1.4%
P2	21.2%	41.0%
M1	0.7%	0.3%
M2	0.6%	1.2%

Data from Polder *et al.* (2004).

Table 1.4 Frequency of the bilateral absence of teeth.

Tooth	Frequency %	(95% CI)
MAXILLA		
I2	54.0%	(50.9, 57.0)
P2	49.25%	(46.3, 52.2)
MANDIBLE		
I1	41.2%	(30.5, 51.9)
P2	45.6%	(43.5, 47.7)

Data from Polder *et al.* (2004).

Aetiology

Environmental and genetic factors

Several theories concerning the aetiology of hypodontia have been proposed, including suggestions that both genetic and environmental factors may play a role. Hypodontia may appear as an isolated non-syndromic feature or as part of a complex syndrome with developmental defects of other ectodermal organs (Lucas, 2000). Early workers investigating the aetiology of isolated non-syndromic hypodontia proposed an anthropological viewpoint, one that reflected an ongoing process of evolution. Butler's Field Theory for the evolutionary development of mammalian teeth (Butler, 1939), when applied to the human dentition by Dahlberg (1945), suggested that the most mesial tooth in each morphological series was the most genetically stable and consequently was rarely missing. Such teeth were designated as 'key teeth' and included the central incisors, canines, first premolars and first molars. In contrast, teeth at the end of each field showed less genetic stability. This led to the concept of *stable* and *unstable* elements of the dentition (Bailit, 1975).

This principle was further supported by Bolk's Theory of Terminal Reduction (de Beer, 1951; Rózsa *et al.*, 2009). This proposed that the evolutionary process was leading to the reduction of the distal element of tooth groups, resulting in the more frequent absence of second premolars, lateral incisors and third molars (Muller *et al.*, 1970; Jorgenson, 1980; Brook, 1984; Schalk van der Weide *et al.*, 1994; Fekonja, 2005; Gábris *et al.*, 2006; Rózsa *et al.*, 2009).

It was also suggested that intra-uterine conditions were involved, and Bailit (1975) encouraged good maternal antenatal nutrition and medical care, but considered that postnatal nutrition, disease, general health and climatic conditions had little influence on hypodontia. The intra-uterine effects of drugs such as thalidomide have been associated with the development of hypodontia (Axrup *et al.*, 1966) as have radiotherapy and chemotherapy in early infancy (Maguire *et al.*, 1987; Dahllőf *et al.*, 1994; Kaste and Hopkins, 1994; Näsman *et al.*, 1997; Nunn *et al.*, 2003; Oğuz *et al.*, 2004).

Other environmental factors that may cause arrested tooth development include a local effect of trauma, such as alveolar fracture or jaw fracture, jaw surgery or iatrogenic damage to the developing tooth germ from traumatic extraction of the overlying primary tooth (Grahnen, 1956; Nunn *et al.*, 2003).

Hypodontia has also been associated with cleft lip and palate, usually localised to the maxillary lateral incisor in the line of the alveolar cleft (Dhanrajani, 2002). This was initially considered to be a physical obstruction of the developing dental lamina from which the tooth germ develops, however more recently a defect in the *Msx1* gene has been identified, which is associated with both isolated cleft lip and cleft palate, and hypodontia (Satokata and Maas, 1994; van den Boogaard *et al.*, 2000; Alappat *et al.*, 2003).

Although occasionally hypodontia is associated with environmental factors, in the majority of cases it has a genetic basis, which has been the subject of intensive research. Hypodontia is frequently identified as a familial trait, with several generations affected within families, although the genetic mechanisms are still poorly understood. In family studies, a greater frequency of hypodontia has been demonstrated among the relatives of probands than in the general population (Brook, 1984).

As well as the familial nature of hypodontia, it often presents as an isolated diagnosis with no detectable family history, which suggests it can occur as a result of a spontaneous genetic mutation (Kupietzky and Houpt, 1995; Dhanrajani, 2002).

Inheritance patterns

Examination of monozygotic twins and triplets indicates there is a familial pattern in hypodontia (Gravely and Johnson, 1971). This is thought to occur by an autosomal dominant process with incomplete penetrance of up to 86% (Arte and Pirinen, 2004). A polygenic model was proposed that involved interaction between epistatic genes and environmental factors (Suarez and Spence, 1974; Bailit, 1975). A link was also proposed to explain the commonly observed association between hypodontia and microdontia. This multifactorial model (Suarez and Spence, 1974; Brook, 1984) was based on an underlying continuum of tooth size with thresholds, whereby there is a progressive reduction in the size of the tooth which

reaches a certain threshold below which the developing tooth germ degenerates, so producing hypodontia.

Tooth development

Tooth development is a complex process, which commences in the developing embryo as an interaction between the oral epithelium and ectomesenchyme derived from the neural crest. A thickening of the epithelium develops into a dental placode and invagination then occurs to produce a tooth bud (Dassule *et al.*, 2000). A collection of cells within the tooth bud, known as the primary enamel knot, manages this process through genetically controlled signalling pathways (Vaahtokari *et al.*, 1996). The mesenchyme begins to surround the epithelium to initially produce a cap stage, and later a bell stage. Mesenchymal cells adjacent to the basement membrane differentiate into odontoblasts, which begin to secrete an organic dentine matrix into which hydroxyapatite crystals are deposited. The epithelial cells adjacent to the dentine differentiate into ameloblasts, which secrete the enamel matrix and control the mineralisation and subsequent maturation of the enamel (Dassule *et al.*, 2000).

The formation and morphology of the cusps in premolars and molars is controlled by secondary enamel knots, which develop at the sites where the cusps are to form. These produce folding of the developing tooth germ to the pre-determined crown morphology (Zhang *et al.*, 2008). Root formation continues with the formation of dentine under the control of Hertwig's root sheath, which later degenerates and leads to the development of cementoblasts. The cementoblasts, in turn, deposit cementum on the root surface (Nakatomi *et al.*, 2006; Khan *et al.*, 2007). Cells in the adjacent dental follicle differentiate into fibroblasts and osteoblasts, and these cells contribute to the formation of the periodontal ligament (Fleischmannova *et al.*, 2008).

Genes involved in odontogenesis

As can be seen, the development of the dentition is a complex process involving a series of epithelial–mesenchymal interactions, and involving growth factors, transcription factors, signalling pathways and other morphogens (Thesleff, 2000). With such complexity, it is not surprising that disturbances can occur in the process, potentially resulting in tooth agenesis (Kapadia *et al.*, 2007). At the molecular level during odontogenesis, epithelial–mesenchymal signalling is under the control of members of the *Wnt* (wingless), *Hh* (hedgehog), *Fgf* (fibroblast growth factor) and *Bmp* (bone morphogenic protein) gene families (Cobourne, 1999; Dassule *et al.*, 2000). Defects in any of these pathways can result in disorders of tooth number (hypodontia or supernumerary teeth), tooth morphology (tooth size and shape) and tooth mineralisation (amelogenesis imperfecta or dentinogenesis imperfecta) (Fleischmannova *et al.*, 2008).

Of particular interest in hypodontia are the genes called *Msx1* (muscle segment homeobox 1) and *Pax9* (paired box 9), which are homeobox transcription factors involved in early odontogenesis under the control of *Bmp* and *Fgf* signalling (Satokata and Maas, 1994; Vastardis *et al.*, 1996; Dahl, 1998; Lidral and Reising, 2002; Alappat *et al.*, 2003; Mostowska *et al.*, 2003; Nunn *et al.*, 2003; Cobourne, 2007; Kapadia *et al.*, 2007; Fleischmannova *et al.*, 2008; Matalova *et al.*, 2008).

A review by Fleischmannova *et al.* (2008) has highlighted the progress that has been made over the last decade in understanding the genetic basis of hypodontia using the transgenic mouse model incorporating selective gene deletions. These have concentrated on the role of homeobox genes, which were originally identified in the fruit fly, *Drosophila*. Homeobox genes code for specific transcription factors, which regulate downstream target genes. Studies have suggested that mutations in the homeobox genes *Msx1* and *Pax9*, which interact during odontogenesis, are associated with tooth agenesis in mice and may be associated with hypodontia in humans. *Msx1* is expressed in regions of condensing ectomesenchyme within the tooth germ. Mice lacking a functional *Msx1* gene demonstrate arrested tooth development at the bud stage. *Pax9* is expressed in the mesenchymal element of the developing tooth germ and is essential during later stages of tooth development. Mice with targeted mutations of *Pax9* show arrested tooth development at the bud stage. More recently, defects in a third gene, *Axin2,* have been identified as having a possible association with severe hypodontia (Lammi *et al.*, 2004; Cobourne, 2007).

Syndromic associations

Several syndromes exhibit hypodontia as one of their features, and many of these have demonstrated gene defects (*Online Mendelian Inheritance in Man* (OMIM) database). Mutations in the homeobox transcription factor *Pitx2* (paired-like homeodomain transcription factor 2) are associated with Rieger syndrome, an autosomal dominant disorder with ocular, umbilical and dental defects. Mutations in *p63* are associated with syndromes involving hypodontia that include digital disorders like syndactyly and ectrodactyly, facial clefts, cleft lip and palate, and ectodermal dysplasia. Mutations in *Msx1* have also been associated with isolated cleft lip and palate, and Witkop (tooth and nail) syndrome (Jumlongras *et al.*, 2001).

The genetic inheritance of the family of ectodermal dysplasias has been investigated. There are over 190 different types of this condition, and while several genes have been implicated, the exact numbers of genes have yet to be determined. Hypohidrotic ectodermal dysplasia (HED) is a disorder in which the sweat glands are reduced in number, which has received the greatest attention. Defects in the *Xq12–Xq13* site on the X chromosome, which encodes for the protein ectodysplasin-A (*Eda*), have been shown to be associated with an X-linked inheritance pattern (XHED). The same chromosome site defects have been identified in non-syndromic isolated X-linked hypodontia. Mutations in the modulator gene *Nemo*, a downstream target of *Eda* signalling, have also been associated with X-linked HED. *Eda* has a role in epithelial–mesenchymal signalling, and is expressed in the development of the ectodermal structures that develop from epithelial placodes, including skin, sweat glands, hair, nails and teeth. In severe cases, the dental effects can result in anodontia. Hypohidrotic ectodermal dysplasia is also associated with both autosomal dominant and autosomal recessive patterns of inheritance through mutations in the ectodysplasin-A receptor (*Eda-R*), and an autosomal recessive pattern of inheritance through mutations in the EdaR-associated death domain (*Edaradd*).

Studies in mice have shown that defects in the *Eda* pathway result in disorders of tooth number, tooth size and tooth morphology, with a reduction in the number of molar cusps. This suggests a mechanism for the relationship of hypodontia and microdontia, and in particular the conical shape of the teeth in individuals with ectodermal dysplasia. Table 1.5 presents further information relating to syndromes associated with hypodontia, including the current understanding of inheritance patterns, the gene loci associated with the syndrome and affected gene pathways.

The genetic processes and signalling pathways involved in hypodontia are complex and frequently rely on data extrapolated from transgenic mice to humans (Kronmiller *et al.*, 1995; Vaahtokari *et al.*, 1996; Hardcastle *et al.*, 1999; Dassule *et al.*, 2000; Zhang *et al.*, 2000; Cobourne *et al.*, 2001, 2004; Miletich *et al.*, 2005; Nakatomi *et al.*, 2006; Khan *et al.*, 2007; Zhang *et al.*, 2008). Understanding the genetics of hypodontia is important for diagnostic and counselling purposes (Gill *et al.*, 2008) and offers the opportunity of genetic screening for affected families. It also presents the challenges of employing tissue engineering and stem cell technology as therapeutic alternatives. Initial studies have suggested that arrested tooth development in *Pax9*- or *Msx1*-deficient mice can be rescued by the transgenic expression of *Bmp4*, an influential signalling factor in a number of developmental processes (Zhang *et al.*, 2000; Fleischmannova *et al.*, 2008).

Identifying the genes and pathways associated with hypodontia and associated syndromes, opens an exciting possibility for the future, one that may hold the potential for direct postnatal gene therapy on developing tooth germs and the prospect of treating hypodontia at a molecular level (Fleischmannova *et al.*, 2008). This concept has so far been investigated in animal models, whereby teeth have been successfully bioengineered in mice, rats and pigs using stem cell biology and biodegradable scaffolds for potential use in organ replacement therapy (Young *et al.*, 2005a, 2005b; Yelick and Vacanti, 2006; Nakahara and Ide, 2007; Duailibi *et al.*, 2008; Honda *et al.*, 2008; Ikeda and Tsuji, 2008; Ikeda *et al.*, 2009; Zhang *et al.*, 2009).

These developments support the feasibility of bioengineering the formation of replacement teeth in the jaws of humans in the future. Such practical application of bioengineering could provide a novel approach to the management of patients with hypodontia through tissue regenerative therapy.

Table 1.5 Syndromic associations of hypodontia (including genetic data).

Syndrome	Affected areas/structures	Mode of inheritance	Gene map loci	Genes affected
Hypohidrotic ectodermal dysplasia 1 (HED)	Skin, sweat glands, hair, nails, teeth (hypodontia)	X-linked recessive	Xq12–q13.1	Ectodysplasin A (Eda)
Hypohidrotic ectodermal dysplasia 3 (EDA3)	Skin, sweat glands, hair, nails, teeth (hypodontia)	Autosomal dominant	2q11–q13 1q42–q43	Ectodysplasin anhidrotic receptor gene (Edar); EDAR-associated death domain (Edaradd)
Hypohidrotic ectodermal dysplasia with immune deficiency (HED-ID)	Skin, sweat glands, hair, nails, teeth (hypodontia), dysgammaglobulinaemia	X-linked recessive	Xq28	IKK-gamma gene (IKBKG or Nemo)
Incontinentia pigmenti (Bloch–Sulzberger syndrome)	Skin (hyperpigmented patches), hair, eyes, central nervous system, teeth (hypodontia)	Male-lethal X-linked dominant	Xq28	IKK-gamma gene (IKBKG or Nemo)
Ectrodactyly, ectodermal dysplasia and cleft lip/palate syndrome 1 (EEC1)	Digits (split hand/foot), hair, skin, nails, mouth (cleft lip/palate), teeth (hypodontia)	Autosomal dominant	7q11.2–q21.3	TP63
Cleft lip/palate-ectodermal dysplasia syndrome (CLPED1)	Mouth (cleft lip/palate), nails, hair, digits (syndactyly), teeth (hypodontia)	Autosomal recessive	11q23–q24	PVRL 1
Witkop syndrome (tooth and nail syndrome)	Nails, teeth (hypodontia)	Autosomal dominant	4p16.1	Msx1
van der Woude syndrome (lip-pit syndrome)	Mouth (pits in lower lip, cleft lip/palate/ uvula), teeth (hypodontia)	Autosomal dominant	1q32–q41	Interferon regulatory factor 6 (IRF6)
Oral–facial–digital syndrome (OFD)	Mouth (cleft palate, cleft tongue), digits (polydactyly), kidneys, central nervous system, teeth (hypodontia)	Male-lethal X-linked dominant	Xp22.3–p22.2	OFD1 protein gene (CXorf5)
Rieger syndrome	Eyes, umbilical cord, growth hormone (deficiency), teeth (hypodontia)	Autosomal dominant	4q25–q26	Paired-like homeodomain transcription factor-2 gene (Pitx2)
Down syndrome (trisomy 21)	Face, eyes, heart, blood (leukaemia), central nervous system, endocrine system, hearing, teeth (hypodontia)	Isolated cases	21q22.3 1q43 Xp11.23	–
Book syndrome	Hair (premature greying), hyperhidrosis,teeth (hypodontia)	Autosomal dominant	–	–
Holoprosencephaly	Cyclopia, face (facial clefts), mouth (cleft lip/palate), midline maxillary central incisor	Autosomal recessive	21q22.3	–

Data from *Online Mendelian Inheritance in Man* (OMIM) at www.ncbi.nlm.nih.gov/Omim/.

Key Points: Definitions, prevalence and aetiology

- Various terms have been used to describe the developmental absence of teeth, including hypodontia, oligodontia and dental agenesis. Hypodontia may present as an isolated condition, or may be associated with syndromes including the ectodermal dysplasias.
- Prevalence varies between continents, racial groups and genders. In Caucasians, the prevalence is 4–6% with a female to male ratio of approximately 3 : 2.
- A number of homeobox genes associated with tooth development have been implicated in the aetiology of hypodontia, including *Msx1*, *Pax9* and *Axin2*. Gene therapy may offer the potential for bioengineering of replacement teeth as a novel approach to managing hypodontia.

References

Alappat S, Zhang ZY, Chen YP. *Msx* homeobox gene family and craniofacial development. *Cell Res* 2003;13: 429–442.

Arte S, Pirinen S. Hypodontia. *Orphanet Encyclopedia* 2004. Available at www.orpha.net/data/patho/GB/uk-hypodontia.pdf [/](last accessed July 2010.

Axrup K, D'Avignon M, Hellgren K, *et al.* Children with thalidomide embryopathy: odontological observations and aspects. *Acta Odontol Scand* 1966;24:3–21.

Bailit HL. Dental variation among populations. An anthropologic view. *Dent Clin North Am* 1975;19:125–139.

Brook AH. A unifying aetiological explanation for anomalies of human tooth number and size. *Arch Oral Biol* 1984;29:373–378.

Butler PM. Studies of the mammalian dentition. Differentiation of the post-canine dentition. *Proc Zoolog Soc Lond* 1939;109B:1–36.

Carvalho JC, Vinker F, Declerck D. Malocclusion, dental injuries and dental anomalies in the primary dentition of Belgian children. *Int J Paediatr Dent* 1998;8: 137–141.

Cobourne MT. The genetic control of early odontogenesis. *Br J Orthod* 1999;26:21–28.

Cobourne MT. Familial human hypodontia – Is it all in the genes? *Br Dent J* 2007;203:203–208.

Cobourne MT, Hardcastle Z, Sharpe PT. *Sonic hedgehog* regulates epithelial proliferation and cell survival in the developing tooth germ. *J Dent Res* 2001;80:1974–1979.

Cobourne MT, Miletich I, Sharpe PT. Restriction of *sonic hedgehog* signalling during early tooth development. *Development* 2004;131:2875–2885.

Dahl N. Genetics of ectodermal dysplasia syndromes. In: B Bergendal, G Koch, J Kurol, G Wänndahl (eds) *Consensus Conference on Ectodermal Dysplasia with Special Reference to Dental Treatment*. Gothia, Stockholm, 1998, pp. 22–31.

Dahlberg AA. The changing dentition of man. *J Am Dent Assoc* 1945;32:676–690.

Dahllőf G, Rozell B, Forsberg CM, Borgström B. Histologic changes in dental morphology induced by high dose chemotherapy and total body irradiation. *Oral Surg Oral Med Oral Pathol* 1994;77:56–60.

Dassule HR, Lewis P, Bei M, Maas R, McMahon AP. *Sonic hedgehog* regulates growth and morphogenesis of the tooth. *Development* 2000;127:4775–4785.

Daugaard-Jensen J, Nodal M, Skovgaard LT, Kjaer I. Comparison of the pattern of agenesis in the primary and permanent dentitions in a population characterized by agenesis in the primary dentition. *Int J Paediatr Dent* 1997;7:143–148.

de Beer GR. *Embryos and Ancestors*. Clarendon Press, Oxford 1951; pp 58–59.

Dhanrajani PJ. Hypodontia: Etiology, clinical features, and management. *Quintessence Int* 2002;33:294–302.

Duailibi SE, Duailibi MT, Zhang W, *et al*. Bioengineered dental tissues grown in the rat jaw. *J Dent Res* 2008;87: 745–750.

Egermark-Eriksson I, Lind V. Congenital numerical variation in the permanent dentition. Sex distribution of hypodontia and hyperodontia. *Odontol Revy* 1971;22: 309–315.

Endo T, Ozoe R, Kubota M, Akiyama M, Shimooka S. A survey of hypodontia in Japanese orthodontic patients. *Am J Orthod Dentofacial Orthop* 2006a;129:29–35.

Endo T, Ozoe R, Yoshino S, Shimooka S. Hypodontia patterns and variations in craniofacial morphology in Japanese orthodontic patients. *Angle Orthod* 2006b;76: 996–1003.

Fekonja A. Hypodontia in orthodontically treated children. *Eur J Orthod* 2005;27:457–460.

Ferguson JW. IOTN (DHC): Is it supported by evidence? *Dent Update* 2006;33:478–486.

Fleischmannova J, Matalova E, Tucker AS, Sharpe PT. Mouse models of tooth abnormalities. *Eur J Oral Sci* 2008;116:1–10.

Flores-Mir C. More women in Europe and Australia have dental agenesis than their counterparts in North America. *Evid Based Dent* 2005;6:22–23.

Forgie AH, Thind BS, Larmour CJ, Mossey PA, Stirrups DR. Management of hypodontia: restorative considerations. Part III. *Quintessence Int* 2005;36: 437–445.

Gábris K, Fábián G, Kaán M, Rózsa N, Tarján I. Prevalence of hypodontia and hyperdontia in paedodontic and orthodontic patients in Budapest. *Community Dent Health* 2006;23:80–82.

Gill DS, Jones S, Hobkirk J, *et al*. Counselling patients with hypodontia. *Dent Update* 2008;35:344–352.

Goodman JR, Jones SP, Hobkirk JA, King PA. Hypodontia:1. Clinical features and the management of mild to moderate hypodontia. *Dent Update* 1994;21:381–384.

Grahnen H. Hypodontia in the permanent dentition. A clinical and genetical investigation. *Odontol Revy* 1956; 7(Suppl.3):1–100.

Grahnen H, Granath LE. Numerical variations in primary dentition and their correlation with the permanent dentition. *Odontol Revy* 1961;12:348–357.

Gravely JF, Johnson, DB. Variation in the expression of hypodontia in monozygotic twins. *Dent Pract Dent Rec* 1971;21:212–220.

Hardcastle Z, Hui CC, Sharpe PT. The *Shh* signalling pathway in early tooth development. *Cell Mol Biol* 1999;45:567–578.

Hobkirk JA, Brook AH. The management of patients with severe hypodontia. *J Oral Rehabil* 1980;7: 289–298.

Hobkirk JA, Nohl F, Bergendal B, Storhaug K, Richter MK. The management of ectodermal dysplasia and severe hypodontia. International conference statements. *J Oral Rehabil* 2006;33:634–637.

Hobson RS, Carter NE, Gillgrass TJ, *et al*. The interdisciplinary management of hypodontia: The relationship between an interdisciplinary team and the general dental practitioner. *Br Dent J* 2003;194:479–482.

Honda MJ, Fong H, Iwatsuki S, Sumita Y, Sarikaya M. Tooth-forming potential in embryonic and postnatal tooth bud cells. *Med Mol Morphol* 2008;41:183–192.

Ikeda E, Tsuji T. Growing bioengineered teeth from single cells: potential for dental regenerative medicine. *Expert Opin Biol Ther* 2008;8:735–744.

Ikeda E, Morita R, Nakao K, *et al*. Fully functional bioengineered tooth replacement as an organ replacement therapy. *Proc Natl Acad Sci USA* 2009;106:13475–13480.

Järvinen S, Lehtinen L. Supernumerary and congenitally missing primary teeth in Finnish children. An epidemiologic study. *Acta Odontol Scand* 1981;39:83–86.

Jones SP. The multidisciplinary management of hypodontia. *Dental Nursing* 2009;5:678–682.

Jorgenson RJ. Clinician's view of hypodontia. *J Am Dent Assoc* 1980;101:283–286.

Jumlongras D, Bei M, Stimson JM, *et al*. A nonsense mutation in *MSX1* causes Witkop syndrome. *Am J Hum Genet* 2001;69:67–74.

Kapadia H, Mues G, D'Souza R. Genes affecting tooth morphogenesis. *Orthod Craniofac Res* 2007;10:237–244.

Kaste SC, Hopkins KP. Micrognathia after radiation therapy for childhood facial tumors. Report of two cases with long-term follow-up. *Oral Surg Oral Med Oral Pathol* 1994;77:95–99.

Khan M, Seppala M, Zoupa M, Cobourne MT. *Hedgehog* pathway gene expression during early development of the molar tooth root in the mouse. *Gene Expr Patterns* 2007;7:239–243.

Kronmiller JE, Nguyen T, Berndt W, Wickson A. Spatial and temporal distribution of *sonic hedgehog* mRNA in the embryonic mouse mandible by reverse transcription/polymerase chain reaction and in situ hybridization analysis. *Arch Oral Biol* 1995;40: 831–838.

Kupietzky A, Houpt M. Hypohidrotic ectodermal dysplasia: characteristics and treatment. *Quintessence Int* 1995;26:285–291.

Lammi L, Arte S, Somer M, *et al*. Mutations in *AXIN2* cause familial tooth agenesis and predispose to colorectal cancer. *Am J Hum Genet* 2004;74:1043–1050.

Larmour CJ, Mossey PA, Thind BS, Forgie AH, Stirrups DR. Hypodontia - a retrospective review of prevalence and etiology. Part I. *Quintessence Int* 2005;36:263–270.

Lidral AC, Reising BC. The role of *MSX1* in human tooth agenesis. *J Dent Res* 2002;81:274–278.

Lucas J. The syndromic tooth–the aetiology, prevalence, presentation and evaluation of hypodontia in children with syndromes. *Ann R Australas Coll Dent Surg* 2000; 15:211–217.

Maguire A, Craft AW, Evans RG, *et al*. The long-term effects of treatment on the dental condition of children surviving malignant disease. *Cancer* 1987;60: 2570–2575.

Matalova E, Fleischmannova J, Sharpe PT, Tucker AS. Tooth agenesis: from molecular genetics to molecular dentistry. *J Dent Res* 2008;87:617–623.

Miletich I, Cobourne MT, Abdeen M, Sharpe PT. Expression of the *Hedgehog* antagonists *Rab23* and *Slimb/betaTrCP* during mouse tooth development. *Arch Oral Biol* 2005;50:147–151.

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.

Muller TP, Hill IN, Petersen AC, Blayney JR. A survey of congenitally missing permanent teeth. *J Am Dent Assoc* 1970;81:101–107.

Nakahara T, Ide Y. Tooth regeneration: implications for the use of bioengineered organs in first-wave organ replacement. *Hum Cell* 2007;20:63–70.

Nakatomi M, Morita I, Eto K, Ota MS. *Sonic hedgehog* signaling is important in tooth root development. *J Dent Res* 2006;85:427–431.

Näsman M, Forsberg CM, Dahllöf G. Long-term dental development in children after treatment for malignant disease. *Eur J Orthod* 1997;19:151–159.

Niswander JD, Sujaku C. Congenital anomalies of teeth in Japanese children. *Am J Phys Anthropol* 1963;21: 569–574.

Nunn JH, Carter NE, Gillgrass TJ, *et al*. The interdisciplinary management of hypodontia: background

and role of paediatric dentistry. *Br Dent J* 2003;194: 245–251.

Oğuz A, Cetiner S, Karadeniz C, *et al*. Long-term effects of chemotherapy on orodental structures in children with non-Hodgkin's lymphoma. *Eur J Oral Sci* 2004; 112:8–11.

Online Mendelian Inheritance in Man (OMIM). Available at: www.ncbi.nlm.nih.gov/Omim/ (last accessed July 2010).

Otuyemi OD, Jones SP. Methods of assessing and grading malocclusion: A review. *Aust Orthod J* 1995;14: 21–27.

Polder BJ, Van't Hof MA, Van der Linden FPGM, Kuijpers-Jagtman AM. A meta-analysis of the prevalence of dental agenesis of permanent teeth. *Community Dent Oral Epidemiol* 2004;32:217–226.

Rózsa N, Nagy K, Vajó Z, *et al*. Prevalence and distribution of permanent canine agenesis in dental paediatric and orthodontic patients in Hungary. *Eur J Orthod* 2009;31:374–379.

Satokata I, Maas R. *MSX1* deficient mice exhibit cleft palate and abnormalities of craniofacial and tooth development. *Nat Genet* 1994;6:348–356.

Schalk van der Weide Y, Beemer FA, Faber JAJ, Bosman F. Symptomatology of patients with oligodontia. *J Oral Rehabil* 1994;21:247–261.

Schalk van der Weide Y, Steen WH, Bosman F. Distribution of missing teeth and tooth morphology in patients with oligodontia. *J Dent Child* 1992;59:133–140.

Shaw WC, Richmond S, O'Brien KD, Brook P, Stephens CD. Quality control in orthodontics: Indices of treatment need and treatment standards. *Br Dent J* 1991; 170:107–112.

Shelton AT, Hobson RS, Slater D. A preliminary evaluation of pre-treatment hypodontia patients using the Dental Aesthetic Index: how does it compare with other commonly used indices? *Eur J Orthod* 2008;30: 244–248.

Suarez BK, Spence MA. The genetics of hypodontia. *J Dent Res* 1974;53:781–785.

Thesleff I. Genetic basis of tooth development and dental defects. *Acta Odontol Scand* 2000;58:191–194.

Thind BS, Stirrups DR, Forgie AH, Larmour CJ, Mossey PA. Management of hypodontia: orthodontic considerations. (II). *Quintessence Int* 2005;36:345–353.

Vaahtokari A, Aberg T, Jernvall J, Keränen S, Thesleff I. The enamel knot as a signaling center in the developing mouse tooth. *Mech Dev* 1996;54:39–43.

van den Boogaard MJ, Dorland M, Beemer FA, van Amstel HK. *MSX1* mutation is associated with orofacial clefting and tooth agenesis in humans. *Nat Genet* 2000;24:342–343.

Vastardis H, Karimbux N, Guthua SW, Seidman JG, Seidman CE. A human *MSX1* homeodomain missense mutation causes selective tooth agenesis. *Nat Genet* 1996;13:417–421.

Waring D, Jones JW. Does the GDP need to know about IOTN? *Dent Update* 2003;30:123–130.

Whittington BR, Durward CS. Survey of anomalies in primary teeth and their correlation with the permanent dentition. *N Z Dent J* 1996;92:4–8.

Yelick PC, Vacanti JP. Bioengineered teeth from tooth bud cells. *Dent Clin North Am* 2006;50:191–203.

Young CS, Abukawa H, Asrican R, *et al*. Tissue-engineered hybrid tooth and bone. *Tissue Eng* 2005a; 11:1599–1610.

Young CS, Kim SW, Qin C, *et al*. Developmental analysis and computer modelling of bioengineered teeth. *Arch Oral Biol* 2005b;50:259–265.

Zhang L, Hua F, Yuan GH, Zhang YD, Chen Z. *Sonic hedgehog* signaling is critical for cytodifferentiation and cusp formation in developing mouse molars. *J Mol Histol* 2008;39:87–94.

Zhang W, Abukawa H, Troulis MJ, *et al*. Tissue engineered hybrid tooth-bone constructs. *Methods* 2009;47: 122–128.

Zhang Y, Zhang Z, Zhao X, *et al*. A new function of *BMP4*: dual role for *BMP4* in regulation of *Sonic hedgehog* expression in the mouse tooth germ. *Development* 2000;127:1431–1443.