

Hypodontia

A Team Approach to Management

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Introduction

This book has its origins in the establishment in 1977 of a multidisciplinary hypodontia clinic at the Eastman Dental Hospital in London. In subsequent years both the number of clinicians in the team and their range of activities has expanded such that by 2007 over 3000 patients had been treated. They and their patients' collective journeys form the basis of this book.

This text has been written for senior undergraduate students, graduate students and specialist trainees from the range of specialisms that can form part of a multidisciplinary hypodontia team, and it assumes a basic level of knowledge of subjects outside a given speciality. Its aim is to develop greater knowledge and understanding of the causes and features of hypodontia, the key issues in its management, and potential approaches to helping those with the condition at the various stages of dental development. Throughout the book emphasis is placed on the potential contributions of the different members of the hypodontia team, and the manner in which each of these can contribute to an integrated care pathway for the patient throughout their life.

The text has been divided into three broad areas, namely background topics, key issues, and age-related approaches to treatment. The content of each of these sections has been influenced by the views of the entire team, as would occur in a hypodontia clinic. Consequently there are cross-refer-

ences between the various chapters, with some topics appearing in different contexts for the sake of clarity and completeness. This avoids needless movement between sections when reading a particular chapter.

The first section, on background topics, considers issues that are fundamental to treatment. It addresses the aetiology and prevalence of hypodontia and the troublesome issue of terminology. The characteristics of the condition are also explored and the section concludes by considering the various ways in which treatment for patients with hypodontia might best be organised using both a specialist hypodontia team and local care providers.

Key issues are addressed in the second section, exploring the fundamentals of space, occlusion and supporting tissues. Assessment and management of space are major factors in the treatment of patients with hypodontia since the size and distribution of space largely determine the feasibility of many treatment procedures and their final outcomes. Modifications to spaces within the arches and between opposing teeth may require orthodontic, prosthodontic and surgical approaches, guided by a clear collective understanding of the ultimate treatment objectives. Patients with hypodontia frequently require treatment that necessitates changes to their occlusion and which may employ a range of principles, philosophies and techniques as work

progresses. Hypodontia is characterised not only by missing teeth but also by deficits in the tissues that are often used to support fixed and removable prostheses; their significance and potential management are also considered in this section.

The third section brings the first two together in the context of treating patients with hypodontia, drawing on the contributions that various specialisms may collectively make to achieve the optimum outcome. While treatment is in practice a continuum, the section has been divided into chapters that consider patients in three consecutive stages of dental development: firstly the primary/early mixed dentition, secondly the late mixed dentition/early permanent dentition, and thirdly the established dentition with hypodontia.

The lists of key points found in every chapter are intended to help readers who are revising and provide a link between chapters, each of which also has its own list of references. These references contribute to an evidence-based approach, supporting various statements in the text and pointing the reader towards further reading. Individual references are not unique to any one chapter since some issues are referred to in more than one context.

Working within a multidisciplinary team can be an extremely rewarding experience both for clinicians and for their patients; it is the authors' hope that readers will find this book of help in initiating, developing and running such clinics.

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; Dahllöf *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	<i>Xq12–q13.1</i>	Ectodysplasin A (<i>Eda</i>)
Hypohidrotic ectodermal dysplasia 3 (<i>EDA3</i>)	Skin, sweat glands, hair, nails, teeth (hypodontia)	Autosomal dominant	<i>2q11–q13</i> <i>1q42–q43</i>	Ectodysplasin anhidrotic receptor gene (<i>Edar</i>); EDAR-associated death domain (<i>Edaradd</i>)
Hypohidrotic ectodermal dysplasia with immune deficiency (HED-ID)	Skin, sweat glands, hair, nails, teeth (hypodontia), dysgammaglobulinaemia	X-linked recessive	<i>Xq28</i>	IKK-gamma gene (<i>IKBKG</i> or <i>Nemo</i>)
Incontinentia pigmenti (Bloch–Sulzberger syndrome)	Skin (hyperpigmented patches), hair, eyes, central nervous system, teeth (hypodontia)	Male-lethal X-linked dominant	<i>Xq28</i>	IKK-gamma gene (<i>IKBKG</i> or <i>Nemo</i>)
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	<i>7q11.2–q21.3</i>	<i>TP63</i>
Cleft lip/palate-ectodermal dysplasia syndrome (CLPED1)	Mouth (cleft lip/palate), nails, hair, digits (syndactyly), teeth (hypodontia)	Autosomal recessive	<i>11q23–q24</i>	<i>PVRL 1</i>
Witkop syndrome (tooth and nail syndrome)	Nails, teeth (hypodontia)	Autosomal dominant	<i>4p16.1</i>	<i>Msx1</i>
van der Woude syndrome (lip-pit syndrome)	Mouth (pits in lower lip, cleft lip/palate/uvula), teeth (hypodontia)	Autosomal dominant	<i>1q32–q41</i>	Interferon regulatory factor 6 (<i>IRF6</i>)
Oral–facial–digital syndrome (OFD)	Mouth (cleft palate, cleft tongue), digits (polydactyly), kidneys, central nervous system, teeth (hypodontia)	Male-lethal X-linked dominant	<i>Xp22.3–p22.2</i>	OFD1 protein gene (<i>CXorf5</i>)
Rieger syndrome	Eyes, umbilical cord, growth hormone (deficiency), teeth (hypodontia)	Autosomal dominant	<i>4q25–q26</i>	Paired-like homeodomain transcription factor-2 gene (<i>Pitx2</i>)
Down syndrome (trisomy 21)	Face, eyes, heart, blood (leukaemia), central nervous system, endocrine system, hearing, teeth (hypodontia)	Isolated cases	<i>21q22.3</i> <i>1q43</i> <i>Xp11.23</i>	–
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	<i>21q22.3</i>	–

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.

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