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
Hypodontia: A Team Approach to Management

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

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

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

*By convention, third molars are excluded from the definition.
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>
<thead>
<tr>
<th>Ethnic group</th>
<th>Mean % males (CI)</th>
<th>Mean % females (CI)</th>
<th>Male to female ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>European (white)</td>
<td>4.6% (4.5, 4.8)</td>
<td>6.3% (6.1, 6.5)</td>
<td>1:1.4</td>
</tr>
<tr>
<td>North American (white)</td>
<td>3.2% (2.9, 3.5)</td>
<td>4.6% (4.2, 4.9)</td>
<td>1:1.4</td>
</tr>
<tr>
<td>North American (African-American)</td>
<td>3.2% (2.2, 4.1)</td>
<td>4.6% (3.5, 5.8)</td>
<td>1:1.4</td>
</tr>
<tr>
<td>Australian (white)</td>
<td>5.5% (4.4, 6.6)</td>
<td>7.6% (6.0, 9.2)</td>
<td>1:1.4</td>
</tr>
<tr>
<td>Saudi Arabian (white)</td>
<td>2.7% (2.0, 3.4)</td>
<td>2.2% (1.2, 3.1)</td>
<td>1:0.8</td>
</tr>
<tr>
<td>Chinese (Mongoloid)</td>
<td>6.1% (4.0, 8.1)</td>
<td>7.7% (5.4, 10.0)</td>
<td>1:1.3</td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>Tooth</th>
<th>Maxilla</th>
<th>Mandible</th>
</tr>
</thead>
<tbody>
<tr>
<td>I1</td>
<td>0.2%</td>
<td>3.5%</td>
</tr>
<tr>
<td>I2</td>
<td>22.9%</td>
<td>2.5%</td>
</tr>
<tr>
<td>C</td>
<td>1.3%</td>
<td>0.3%</td>
</tr>
<tr>
<td>P1</td>
<td>2.8%</td>
<td>1.4%</td>
</tr>
<tr>
<td>P2</td>
<td>21.2%</td>
<td>41.0%</td>
</tr>
<tr>
<td>M1</td>
<td>0.7%</td>
<td>0.3%</td>
</tr>
<tr>
<td>M2</td>
<td>0.6%</td>
<td>1.2%</td>
</tr>
</tbody>
</table>

Data from Polder et al. (2004).

### Table 1.4 Frequency of the bilateral absence of teeth.

<table>
<thead>
<tr>
<th>Tooth</th>
<th>Frequency %</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAXILLA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I2</td>
<td>54.0%</td>
<td>(50.9, 57.0)</td>
</tr>
<tr>
<td>P2</td>
<td>49.25%</td>
<td>(46.3, 52.2)</td>
</tr>
<tr>
<td>MANDIBLE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I1</td>
<td>41.2%</td>
<td>(30.5, 51.9)</td>
</tr>
<tr>
<td>P2</td>
<td>45.6%</td>
<td>(43.5, 47.7)</td>
</tr>
</tbody>
</table>

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; Näsmann et al., 1997; Nunn et al., 2003; Ögüz 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; Vahtokari 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; Yellick 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>
<thead>
<tr>
<th>Syndrome</th>
<th>Affected areas/structures</th>
<th>Mode of inheritance</th>
<th>Gene map loci</th>
<th>Genes affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypohidrotic ectodermal dysplasia 1 (HED)</td>
<td>Skin, sweat glands, hair, nails, teeth (hypodontia)</td>
<td>X-linked recessive</td>
<td>Xq12–q13.1</td>
<td>Ectodysplasin A (Eda)</td>
</tr>
<tr>
<td>Hypohidrotic ectodermal dysplasia 3 (EDA3)</td>
<td>Skin, sweat glands, hair, nails, teeth (hypodontia)</td>
<td>Autosomal dominant</td>
<td>2q11–q13, 1q42–q43</td>
<td>Ectodysplasin anhidrotic receptor gene (Edar); EDAR-associated death domain (Edaradd)</td>
</tr>
<tr>
<td>Hypohidrotic ectodermal dysplasia with immune deficiency (HED-ID)</td>
<td>Skin, sweat glands, hair, nails, teeth (hypodontia), dysgammaglobulinaemia</td>
<td>X-linked recessive</td>
<td>Xq28</td>
<td>IKK-gamma gene (IKBKG or Nemo)</td>
</tr>
<tr>
<td>Incontinentia pigmenti (Bloch–Sulzberger syndrome)</td>
<td>Skin (hyperpigmented patches), hair, eyes, central nervous system, teeth (hypodontia)</td>
<td>Male-lethal X-linked dominant</td>
<td>Xq28</td>
<td>IKK-gamma gene (IKBKG or Nemo)</td>
</tr>
<tr>
<td>Ectrodactyly, ectodermal dysplasia and cleft lip/palate syndrome 1 (EEC1)</td>
<td>Digits (split hand/foot), hair, skin, nails, mouth (cleft lip/palate), teeth (hypodontia)</td>
<td>Autosomal dominant</td>
<td>7q11.2–q21.3</td>
<td>TP63</td>
</tr>
<tr>
<td>Cleft lip/palate-ectodermal dysplasia syndrome (CLPED1)</td>
<td>Mouth (cleft lip/palate), nails, hair, digits (syndactyly), teeth (hypodontia)</td>
<td>Autosomal recessive</td>
<td>11q23–q24</td>
<td>PVRL 1</td>
</tr>
<tr>
<td>Witkop syndrome (tooth and nail syndrome)</td>
<td>Nails, teeth (hypodontia)</td>
<td>Autosomal dominant</td>
<td>4p16.1</td>
<td>Msx1</td>
</tr>
<tr>
<td>van der Woude syndrome (lip-pit syndrome)</td>
<td>Mouth (pits in lower lip, cleft lip/palate/uvula), teeth (hypodontia)</td>
<td>Autosomal dominant</td>
<td>1q32–q41</td>
<td>Interferon regulatory factor 6 (IRF6)</td>
</tr>
<tr>
<td>Oral-facial–digital syndrome (OFD)</td>
<td>Mouth (cleft palate, cleft tongue), digits (polydactyly), kidneys, central nervous system, teeth (hypodontia)</td>
<td>Male-lethal X-linked dominant</td>
<td>Xp22.3–p22.2</td>
<td>OFD1 protein gene (CXorf5)</td>
</tr>
<tr>
<td>Rieger syndrome</td>
<td>Eyes, umbilical cord, growth hormone (deficiency), teeth (hypodontia)</td>
<td>Autosomal dominant</td>
<td>4q25–q26</td>
<td>Paired-like homeodomain transcription factor-2 gene (Pitx2)</td>
</tr>
<tr>
<td>Down syndrome (trisomy 21)</td>
<td>Face, eyes, heart, blood (leukaemia), central nervous system, endocrine system, hearing, teeth (hypodontia)</td>
<td>Isolated cases</td>
<td>21q22.3, 1q43, Xp11.23</td>
<td>–</td>
</tr>
<tr>
<td>Book syndrome</td>
<td>Hair (premature greying), hyperhidrosis, teeth (hypodontia)</td>
<td>Autosomal dominant</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Holoprosencephaly</td>
<td>Cyclopia, face (facial clefts), mouth (cleft lip/palate), midline maxillary central incisor</td>
<td>Autosomal recessive</td>
<td>21q22.3</td>
<td>–</td>
</tr>
</tbody>
</table>

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**


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


