Hypodontia

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Abstract
Congenital lack of one or more teeth is a common anomaly in man. Lack of one or a few permanent teeth, hypodontia, without any systemic disorders is the mildest and most common phenotype. Second premolars and upper lateral incisors are the teeth most frequently affected. The same teeth are also often lacking in the more severe phenotype, oligodontia. Congenital lack of all teeth, anodontia, without associated abnormalities is extremely rare.
Both environmental and genetic factors can cause failure of tooth development. Children treated for malignant diseases at tooth-developing ages show a high frequency of missing teeth. Irradiation produces more severe effects than chemotherapeutic agents
Numerous different genes have been implicated in tooth development by gene expression and experimental studies in the mouse, and in theory, any of these genes may cause tooth agenesis. Family studies show that, as an isolated form, both hypodontia and oligodontia are inherited as an autosomal dominant trait with incomplete penetrance and variable expression. Sex-linked and polygenic or multifactorial models of inheritance have also been suggested. An autosomal recessive model has been shown in some families.
Variability in expression includes the number and region of missing teeth, and various other dental features associated with the trait.
It is evident that both hypodontia and oligodontia are genetically heterogeneous traits. Several different mutations in two transcription factors, MSX1 and PAX9, have been identified in families with dominant oligodontia. A nonsense mutation in the b-catenin binding protein AXIN2 has recently been detected to cause familial oligodontia and predisposing to colorectal neoplasia.

Keywords
Congenitally missing teeth, tooth agenesis, hypodontia, oligodontia, anodontia, incisor-premolar hypodontia, tooth abnormalities, tooth development, dental genetics, *MSX1, PAX9, AXIN2*

Disease name and synonyms

Hypodontia is the term most frequently used when describing the phenomenon of congenitally missing teeth in general. Many other terms appear in the literature to describe a reduction in number of teeth: **oligodontia, anodontia, aplasia of teeth, congenitally missing teeth, absence of teeth, agenesis of teeth, and lack of teeth.**

Hypodontia and oligodontia are classified as **isolated or nonsyndromic hypodontia/oligodontia** and **syndromic hypodontia/oligodontia** or **hypodontia/oligodontia associated with syndromes**.
The term **hypodontia** is used in a narrow sense when the number of missing teeth is one or a few. **Oligodontia** is defined as missing a large

number of teeth. **Anodontia** is an extreme case, denoting complete absence of teeth. There is no clear definition in the literature concerning the limits of these classes. In the recent years, however, the following definitions have been used:
Hypodontia: 1 to 6 teeth missing (excluding the third molars)
Oligodontia: more than six teeth missing (excluding the third molars)
Anodontia: complete absence of teeth.
Incisors and premolars are the most frequently missing teeth. Therefore incisor-premolar hypodontia (IPH) is the term to describe this form of the anomaly.

Definition/Diagnosis Criteria
A tooth is defined to be congenitally missing if it has not erupted in the oral cavity and is not visible in a radiograph. All primary teeth have erupted by the age of 3 and all permanent teeth except the third molars between the ages of 12 and 14. Therefore, 3- to 4-year-old children are suitable for diagnosis of congenitally missing primary teeth by clinical examination, and 12- to 14-year-old children, for diagnosis of permanent teeth, excluding the third molars. Radiographic diagnosis can be made at younger age depending on tooth group. The use of panoramic radiography is recommended, together with clinical examination in detecting or confirming dental development (Pirinen and Thesleff, 1995). All **primary teeth** and the crypts of first permanent molars are visible by radiograph at birth. The crowns of first premolars, second premolars, and second permanent molars start to mineralize near the second birthday, and all **permanent tooth** crowns except the third molars have begun their mineralization by the age of six. The formation of third molars shows very large variation. Usually at the age of 8 to 10 years, the first signs of the third molars appear on a radiograph but occasionally, very late appearance (age 14 to 18) occurs (Pirinen and Thesleff, 1995). The formation of dentition continues many years, and differences exist in mineralization stages among children depending on race, on gender, and even on family and on the individual. Especially second premolars may show late onset of mineralization, and give a false-positive diagnosis of hypodontia in radiographs. Therefore, diagnosis of tooth agenesis in the permanent dentition should be made after the age of 6 (Pirinen and Thesleff, 1995) excluding third molars, and after 10 years of age if third molars are also studied.

Frequency
Primary dentition
Variation in the number of teeth is not as common in the primary as in the permanent dentition, and no significant difference exists in prevalence of hypodontia by gender (Grahnen and Granath, 1961; Ravn, 1971; Järvinen and Lehtinen, 1981). The prevalence varies from 0.4% to 0.9% in the European population (Grahnen and Granath, 1961; Ravn, 1971; Järvinen and Lehtinen, 1981; Magnusson, 1984; Carvalho, 1998), and is reported to be higher, 2.4%, in Japan (Yonezu et *al.*, 1997). Mostly one (55% of the children, according to Daugaard-Jensen et *al.*, 1997) or two teeth are missing, and the upper lateral incisors seem to be affected most often. A strong correlation exists between hypodontia in the primary and permanent dentitions. Children with hypodontia in the primary dentition nearly always show hypodontia of the successors.

Nonsyndromic hypodontia in permanent dentition (OMIM 106600 (TM) database)
Numerous studies have appeared on the prevalence of hypodontia in different countries, showing some variation in populations, on continents and among races. The early reports give lower frequencies, ranging from 2.8% in the USA (Byrd, 1943) to 3.4% in Switzerland (Dolder, 1936). The prevalence of hypodontia seems to be lower in North America (3.5%-3.7%) (Muller et *al.*, 1970) than in European countries (6-8%) (Grahnen, 1956; Haavikko, 1971). However, in a Canadian study the frequency of hypodontia was 7.4% (Thompson and Popovich, 1974). In Australia (6.3%) (Lynham, 1990) and Japan (6.6%) (Niswander and Sujaku, 1963) the frequency of hypodontia corresponds to the values for Caucasians in Europe. There is only a little difference in frequency of hypodontia between white and black students in the USA (Muller et *al.*, 1970).
The reported frequency of agenesis of the third molar(s) is higher, varying from 9% to more than 30% (Grahnen, 1956; Haavikko, 1971). In a Finnish study (Haavikko, 1971), one or more third molars were missing in 21% of individuals with no significant gender difference. Furthermore, 71% of the individuals with hypodontia of some other teeth also lacked their third molar(s).
Most authors report a small but not significant predominance of hypodontia in females (Muller, 1970; Haavikko, 1971; Thompson and Popovich, 1974; Magnusson, 1977; Rolling, 1980; Davis, 1987). Statistically significant differences were calculated in some studies (Brook, 1974; Bergström, 1977).

Family studies have shown the frequency of hypodontia and peg-shaped lateral incisor(s) in 1st- and 2nd -degree relatives of the probands to be significantly higher than in the general population (Grahnen, 1956; Chosack et *al.*, 1975; Brook, 1984, Arte et *al.*, 2001).

Nonsyndromic oligodontia in permanent dentition (OMIM 604625, 313500 (TM) database)

Oligodontia, congenital lack of more than six permanent teeth, has a prevalence of 0.08% in a Dutch study (Schalk-van der Weide, 1992), and 0.16% in a Danish study (Rolling and Poulsen, 2001). The difference in the frequency of oligodontia between males and females is not statistically significant, nor is the difference in distribution of missing teeth over maxilla/mandible and left/right sides (Schalk-van der Weide, 1992; Rolling and Poulsen, 2001). However, combining data from 6 studies, females show a higher frequency than males (Rolling and Poulsen, 2001).Two of every three congenitally missing teeth in oligodontia are second premolars or upper lateral incisors (Rolling and Poulsen, 2001). Oligodontia, like hypodontia, is seen as an isolated trait or as a part of a syndrome. Isolated oligodontia is inherited in an autosomal dominant form with reduced penetrance. Oligodontia and hypodontia have similar associated anomalies with a tendency toward delayed tooth formation, reduced size of teeth, and taurodontism. In a Dutch study of patients with oligodontia, 28.9% showed taurodontism of one or two mandibular first molars, while 9.9% of the control subjects had taurodontism (Schalk-van der Weide, 1992).

Anodontia (OMIM 206780 (TM) database)

Congenital lack of all teeth without associated abnormalities is extremely rare. Some case reports of anodontia have suggested autosomal recessive inheritance (Gorlin et *al.*, 1980). Anodontia occurs as an extreme dental phenotype in ectodermal dysplasia syndromes.

Clinical description

The mandibular second premolar is, in most studies, the most frequently missing tooth (excluding third molars), followed by a maxillary lateral incisor or second premolar (Grahnen, 1956; Haavikko, 1971; Thompson and Popovich, 1974, Arte et *al.* 2001). Absence of maxillary central incisors, maxillary and mandibular first molars and canines seems to be very rare. No clear difference in congenitally missing teeth has been found between the maxilla and the mandible (Grahnen, 1956; Bergström, 1977; Arte et *al.*, 2001). Unilateral hypodontia is common, with no significant difference between the left and right sides of the jaws (Magnusson, 1977; Lai and Seow, 1989).

Most individuals with hypodontia lack only one or two permanent teeth (Grahnen, 1956; Muller, 1970; Haavikko, 1971; Bergström, 1977).

Associated dental anomalies

Several dental anomalies have been reported together with congenitally missing teeth. These are:

<- *Delayed formation and eruption of teeth* have been found in children with hypodontia or oligodontia but great individual variation has been noticed (Garn et *al.*, 1961; Rune and Sarnäs, 1974; Schalk-van der Weide, 1992).

<- *Reduction in tooth size and form* is apparent in these patients. The more teeth are missing the greater the possibility of clinically apparent microdontia in the same individual and the more reduction measured in remaining tooth crowns (Garn and Lewis, 1970; Brook, 1984).

A most striking example of crown-size reduction associated wih hypodontia is a peg-shaped upper lateral incisor (Grahnen, 1956; Alvesalo and Portin, 1969; Baccetti, 1998)

<- *Ectopic maxillary canines* have an association with hypodontia **(**Becker et *al.*, 1981; Brin et *al.*, 1986; Svinhufvud et *al.*, 1988; Baccetti, 1998;).

The frequency of hypodontia was analyzed in 106 patients treated for ectopic canines and their family members in a Finnish study: 36% of the patients and 20% of the first-degree relatives were missing some permanent teeth (Pirinen et *al.*, 1996).

Peck et *al.* (1996, 1998) reported significantly elevated hypodontia frequencies in individuals with either maxillary canine-first premolar transposition, palatal displacement of the maxillary canine, or mandibular lateral incisor-canine transposition.

<-*Ectopic eruption of other teeth*

Ectopic eruption of the first permanent molar(s) showed a significant association with agenesis of second premolars (Baccetti, 1998). Malpositions of the upper lateral incisors, lower canines, and second premolars have also been noticed to occur more often than in the general population in a Finnish family study (Svinhufvud et *al.*, 1988).

<- *Infraposition of primary molar(s)*

A reciprocal association exists between infraocclusion of primary molars and aplasia of premolars (Bjerklin et *al.*, 1992; Baccetti, 1998). In 18% to 22% of the subjects, aplasia of the second premolars was associated with infraocclusion of the first primary molars (Baccetti, 1998).

<- *Short roots of teeth*

Tooth agenesis has appeared in 46% of individuals with short roots of some permanent

teeth, with maxillary central incisors and premolars the most frequently affected teeth in this condition, called short root anomaly (Lind, 1972; Apajalahti et *al.*, 1999). The missing teeth were mostly the same as shown in hypodontia: upper lateral incisors and second premolars (Apajalahti et *al.*, 1999).

<- *Taurodontism*

Investigations of patients with hypodontia and their relatives have revealed an association of taurodontism with hypodontia (Stenvik et.*al.*,1972; Seow and Lai, 1989; Arte,2001) as well as with oligodontia (Schalk-van der Weide, 1993). The frequency of taurodontism is varying between 35% - 64% in the molars of individuals with hypodontia depending the teeth studied (Seow and Lai, 1989; Arte et *al.*, 2001).Taurodontism of the lower first molar(s) were seen in a Dutch study in 29% of oligodontia patients, compared with 10% of the control group (Schalk-van der Weide, 1993).

- Rotation of premolars and/or maxillary lateral incisors

Significant associations appeared between unilateral agenesis of upper lateral incisors and rotation of of the lateral incisor on the other side of the dental arch, and between unilateral agenesis of premolars and rotation of premolars on the other side of the arch (Baccetti, 1998).

- Enamel hypoplasia, hypocalcification

Ahmad *et al.* (1998) reported a recessively inherited hypodontia, in a large family, mapped to chromosome 16. Affected individuals had associated dental anomalies such as enamel hypoplasia, hypocalcification, and dentinogenesis imperfecta (Ahmad *et al.*, 1998). Baccetti (1998) included enamel hypoplasia in seven types of dental anomalies, the associations of which were investigated in an untreated orthodontic population.

Etiology

Environmental factors

In principle, many environmental factors may cause arrested tooth development. Different kinds of trauma in the dental region such as fractures, surgical procedures on the jaws, and extraction of the preceding primary tooth are mentioned in the literature (for review, Grahnen, 1956; Schalk-van der Weide, 1992).

Developing teeth are irreversibly affected by multiagent chemotherapy and radiation therapy, and effects depend on age of patient and dosage (Näsman et *al.*, 1997). Children after treatment for malignant disease at an early age show arrested root development with short V-shaped roots, roots with premature apical closure, enamel hypoplasia, microdontia, and hypodontia. Irradiation produces more severe effects than those caused by chemotherapeutic agents (Maguire et *al.*,1987; Näsman et *al.*,1997)**.**

Congenitally missing teeth have been reported in children whose mother had used Thalidomide^{R} (N-phthaloylglutamimide) during pregnancy (Axrup et *al.*, 1966). No definite etiologic relationship has been found between hypodontia and systemic diseases or endocrine disturbances (for review, Grahnen, 1956; Schalk- van der Weide, 1992).

Genetic factors

Although tooth agenesis is occasionally caused by environmental factors, in the majority of cases hypodontia has a genetic basis.

In familial hypodontia, the type of inheritance in the majority of families seems to be autosomal dominant with incomplete penetrance and variable expressivity. An autosomal recessive model of inheritance is also possible (Ahmad et *al.*, 1998; Pirinen et *al.*, 2001). Peg-shaped upper lateral incisors are considered to be a modified manifestation of the same genotypes as hypodontia (Grahnen, 1956; Alvesalo and Portin, 1969). Sex-linked inheritance patterns and a polygenic or multifactorial model of inheritance have also been suggested (Suarez and Spence, 1974; Chosack et *al.*, 1975; Brook, 1984; Peck et *al.*, 1993). Female predominance has been reported (Bergström, 1977; Wisth et *al.*, 1974; Stamatiou and Symons, 1991; Kotsomitis et *al.*, 1996), but in most studies the difference does not reach statistical significance (Grahnen, 1956; Haavikko, 1971; Rolling, 1980).

Mutations in transcription factors *MSX1* and *PAX9* have been identified in families with an autosomal dominant oligodontia. A missense mutation was first found by the Vastardis group in the homeodomain of *MSX1* gene in chromosome 4 (4p16) in all affected members of a family with missing second premolars and third molars as a prominent feature (Vastardis et *al.*, 1996). All affected individuals were reported to have had normal primary dentitions. Another mutations in the *MSX1* gene was associated with tooth agenesis and various combinations of cleft lip and/or palate or nail dysplasia (Van den Boogaard et *al.*, 2000; Jumlongras et *al.*, 2001). Several different mutations in another transcription factor gene, *PAX9*, in chromosome 14 (14q21-q13) have been identified in families with oligodontia of most molars (Stockton et *al.*, 2000; Nieminen et *al.*, 2001; Das et *al.*, 2002; 2003; Lammi et *al.*, 2003). Besides missing molars, some individuals also lack their maxillary and/or mandibular second premolars as well as mandibular central incisors. The primary dentition is usually normal.

MSX1 and *PAX9* are expressed in dental mesenchyme after initiation of tooth

development in response to epithelial signals (for review, Thesleff, 2000; Nieminen et *al.*, 2001). Inactivation of *Msx1* and *Pax9* genes in the mouse causes arrested development of teeth at the bud stage and malformations of palate, limb, and pharyngeal pouch derivatives, whereas heterozygous mice develop normal teeth (Satokata and Maas, 1994; Peters et *al.*, 1998). A nonsense muation in the WNT signaling regulator AXIN2 has recently been described in a Finnish family with dominantly inherited severe oligodontia. Risk for colorectal neoplasia appears to be associated with oligodontia in this family (Lammi et al., 2004).

Genetic diagnosis

The known mutations in *MSX1, PAX9* are possible to screen but this analysis is not available on a routine basis, so far, it remains a research tool.

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