Pathology of the Hard Dental Tissues

Dedicated to my beloved wife Beatrice

Pathology of the Hard Dental Tissues

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Introduction

Anomalies of the dental hard tissues are classified according to the time at which they develop:

- Prior to and during the development of the teeth within the jaws
- During the eruption of the teeth
- After the eruption of the teeth.

Prior to and during the development of the teeth within the jaws

Disturbances in odontogenesis *prior to* (that is, a failure of a tooth germ to develop) or *during tooth development* are commonly due to endogenous causes, i.e. causes within the body. The disturbances include deviations in the *number* of teeth, *morphological* anomalies and *structural* abnormalities of enamel and dentine, which are dealt with in Chapters 1, 2 and 3, respectively. The separate discussion of each group of anomalies may suggest that they occur independent of each other, but that is not the case. Anomalies in the size of some teeth, for instance, are probably associated with absence of other teeth,[33 37 79 198 199 455 497] implying a relation between tooth number and size. *Agenesis* of a (wisdom) tooth may be accompanied by delayed development of the premolars in the same or in another quadrant.[200 613] This may be because the number, size and morphology of the teeth are determined by interacting genes.

Traits, which are inherited poly-genetically, are distributed normally in the population (that is, statistically their distribution follows the normal bell curve).[33]

During the eruption of teeth

Anomalies of *eruption* may be due to disturbances in eruption times or the path and site of eruption. These anomalies may have either endogenous or exogenous (cause outside the body) causes and are described in Chapter 4.

After the eruption of the teeth

Post-developmental diseases and disturbances of the dental hard tissues, that is those developing after the eruption of the teeth are described in Chapters 5, 6, 7, 8 and 9. These are mostly caused by exogenous factors, but endogenous causes may also contribute. These disorders include *caries*, which despite a vast decline in incidence, is still likely the most frequently occurring of all diseases. The extensive knowledge that exists about caries warrants a separate book, but the disease cannot be neglected in a general book on dental hard tissue pathology.

Some other post-developmental dental diseases are: *erosion*, which is caused by the action of external acids on the dental hard tissues; *resorption*, which is caused by cells that commonly resorb (break down) the bony tissues; tooth *wear*; and *traumatic* conditions. *Discoloration* of the teeth (Chapter 10) may start in either the developmental or post-developmental phase.

Chapter 11 deals with the *syndromes* in which teeth are involved. For the purposes of this volume, a syndrome is defined as an inherited and causally related complex of somatic abnormalities and, occasionally, mental health and behavioural conditions. Because of the large number of such syndromes, only most commonly occurring ones are discussed in this book. The appendix provides an overview of the *chronology* of the individual teeth.

Additional information, for example, evolutionary aspects of the development of the dentition, about which reader is presumed to possess previous knowledge is presented in a smaller font to distinguish it from the main text.

Genetics

Since odontogenesis is under genetic (and environmental) control, an overview of the basics of genetics is necessary before considering the developmental anomalies.

Each human somatic cell nucleus contains DNA that is packaged into 22 pairs of autosomal chromosomes and one pair of sex chromosomes. The sex chromosome pair

may consist of either X and X (female) or X and Y (male) chromosomes. The chromosomes are composed of the DNA polynucleotide chain, which resembles a spiral staircase (double helix). The DNA together with the mitochondrial chromosomes is called the genome. All hereditary information is transmitted by the genome. From the initial assumed number of 80 000–100 000 genes on the 46 chromosomes, a mere 30 000–35 000 were then estimated to exist,[544] but number of the protein-encoding genes that have been sequenced and mapped appears to be as low as 20 000–25 000.

A gene, which is a cluster of nucleotides within a chromosome, is a biological unit that carries hereditary information. All genes have roughly the same form, but they differ in the order and numbers of their four nucleotide building blocks, i.e. the four bases: adenosine, which is consistently paired with cytosine; and guanine, which is paired with thymine. Altogether, the current genome sequence contains 2.85 billion nucleotides, covering more than 99% of the genome with a very low error rate.[285]

Genes have two parts: the exon is the coding part, but the expression of the gene depends on the non-coding part (intron), the so-called junk-DNA. The introns splice the double helix, which allows the genes to be "read", and thus determine where the reading begins. Part of the function of this junk-DNA is still unknown. Transcription of the chromosomes (genes) by way of enzymatic synthesis of a complementary sequence of RNA nucleotides provides, outside the nucleus, the information necessary to synthesise the large number of different proteins. These proteins make up the trillion human cells, giving rise to the nearly 4000 anatomical structures constituting the body.[509]

Interpretation of family trees

The laws of heredity were first formulated by Mendel in 1865. Mendel had discovered that two "factors" (much later called "genes"), one from the mother and another from the father, determined the traits of their offspring. Genes have a regulatory developmental function, and are transmitted in the same way from generation to generation, the *genotype*. The way in which the genotype becomes manifest, the *phenotype*, varies however, because of the influence of environmental factors and mutations that occur not only between generations, but also between family members and within each individual. Knowledge about the chromosome and mutations responsible for hereditary anomalies is rapidly advancing and increasing.

A gene must be exactly copied: if not, a change in form occurs. Since genes encode protein(s), mutated genes will result in synthesis of abnormal proteins. Among the major kinds of gene mutations are:

- Point mutations – in which one base is substituted for another, for example adenosine for cytosine
- Frameshift mutations – in which one of the bases is deleted or inserted
- Deletions – in which a large segment of DNA is deleted and consequently the protein that the gene encodes for often is missing. Instead of being deleted, an extra (part of) a chromosome may be present.

Let us consider an example. The hereditary trait "hypocalcified enamel" may be designated as "**A**" (capital letter indicating dominant) and normally calcified enamel as "**a**" (lower case letter indicating recessive). All individuals receiving from their parents the combinations **AA** (i.e. both chromosomes of the autosomal pair of chromosomes contain the identical genes **A** and **A** = *homozygote*) or **Aa** (the chromosomes of an autosomal pair contain two different genes **A** and **a** = *heterozygote*) will have hypocalcified enamel (for the effect of "**A**" dominates over the effect of "**a**"). Individuals with both recessive homozygotes **aa** will possess normally calcified enamel.

According to Mendel's laws, the offspring of a father with **Aa** (and thus having sperm cells with either "**A**" or "**a**") and a mother with **aa** (each egg contains "**a**") will possess, in a statistical sense, the combinations of genes as shown in Table 0.1. The probability of a heterozygotic child developing hypocalcified enamel is 50%, due to the union of gametes of unlike genetic constitution. Likewise, the probability of homozygosity and therefore normal calcified enamel is also 50%.

If the X-chromosome of the father has the gene that determines the development of hypocalcified enamel, designated X^A, the possibility of the offsprings' enamel being hypocalcified is shown in Table 0.2. A father (X^AY) with poor-quality enamel cannot have a son with poorly calcified enamel because the son gets his X-chromosome from the mother. But all the daughters will have hypocalcified

Table 0.1 Autosomal inherited hypocalcified enamel (A)

		Father	
		A	**a**
Mother	**a**	Aa	aa
	a	Aa	aa

"A" = hypocalcified enamel; "a" = normal enamel.

Table 0.2 Sex-chromosome (X-bound) inherited hypocalcified enamel

		Father	
		X^A	**Y**
Mother	**X**	XX^A (daughter)	XY (son)
	X	XX^A (daughter)	XY (son)

X^A = hypocalcified enamel.

enamel (Table 0.2). This latter example clearly shows that the mother with X^AX chromosomes will pass on the trait to her sons and daughters in equal proportions, assuming the father does not have X^A. In other words, the probability that a child, either male or female, receives X^A (= hypocalcified enamel) from the mother is 50%.

Based on the foregoing discussion, the following criteria may be used to interpret family trees:

1. Autosomal recessive traits:
   - Equal numbers of sons and daughters inherit the trait.
   - 25% of the second generation will show the trait.
2. Autosomal dominant traits:
   - Equal numbers of sons and daughters inherit the trait.
   - 50% of the offspring will show the trait when one of the parents is affected.
3. Sex-chromosome (X-linked) recessive traits:
   - Sons show the trait more frequently than daughters. In order to become manifest, women have to inherit the recessive gene from both the father and the mother; the daughters are "carriers" when either the father or the mother possesses the mutated gene.
   - The father transmits the defective gene to only his daughters.
4. Sex-chromosome (X-linked) dominant traits:
   - Daughters show the trait twice as often as the sons.
   - The father with the trait transmits it to all his daughters, but not to his sons.
   - The mother transmits the trait to her sons and daughters in equal proportions.
5. Sex-chromosome (X-linked) dominant father and mother:
   - 100% of the daughters will show the trait.
   - 50% of the sons are affected, unless both X-chromosomes of the mother contain the mutant gene, in which case all sons show the trait.
6. When the trait is linked to the Y-chromosome, all the sons will be affected but none of the daughters.

Studies of small groups (e.g. families) will favour the detection of a dominant rather than a recessive gene. Other important points to note are listed below:

- Expressivity – is the way in which an anomaly manifests itself, for instance a reduction in the size of a tooth may be more or less pronounced.
- Penetrance – denotes the proportion of the genotype that is phenotypically manifested. The penetrance is 50% when half of the descendants with the mutated gene show the trait.

Note: expressivity may be regarded as the individual measure and penetrance as the statistical measure.

- Lyon hypothesis – in each cell of a female, only one of the two X-chromosomes functions randomly. Her cells therefore essentially show a "mosaic pattern": in a cell either the X-chromosome of the father or that of the mother will be active;[367] a hereditary effect on the enamel may be represented as vertically alternating rows of normal and abnormal enamel.
- Allele – one of a pair (or series) of genes that may be present on a certain location in the chromosome. For instance, the allele for blue eyes or the allele for brown eyes is located in the same place.
- Polygenetic heredity – a dental trait is determined by more than one gene, for example "**A**" and "**B**" (if recessive, then "**a**" and "**b**").

In such cases, larger numbers of genotypes and phenotypes have to be distinguished. Suppose that two genes determine the tooth size (Table 0.3). After conception, the fertilised egg contains the two responsible genes from the father and the mother. The following combinations, in principle, are possible from the mother: AB, Ab, aB and ab. The same holds true for the two genes from the father. Table 0.3 shows all the possible combinations of genes that may occur in the offspring.[448] Five combinations with 4, 3, 2, 1 or 0 (capital A or B) are possible, thus five phenotypes exist (see the identical numbers in brackets). Table 0.3 also makes clear that the number of genotypes is larger, namely nine. For example, phenotype (4) includes the combinations with three capital letters and one small case letter. Phenotype (4) is present four times in Table 0.3. Altogether, the 16 combinations shown in the table represent nine genotypes.

Seven phenotypes are possible when three genes determine a trait. The number of phenotypes is given by the formula 2k + 1, where k is the number of genes. Ludwig (1957) studied seven morphological traits of the mandibular second premolars in different races and in monozygotic and heterozygotic twins. Many combinations of the traits were evident.[365] The number of genes involved in the initiation, cell proliferation and morphogenesis of the teeth, is however much larger.

Table 0.3 Polygenetic heredity

	Father			
Mother	**AB**	**Ab**	**aB**	**ab**
AB	AB (5) AB	Ab (4) AB	aB (4) AB	ab (3) AB
Ab	AB (4) Ab	Ab (3) Ab	aB (3) Ab	ab (2) Ab
aB	AB (4) aB	Ab (3) aB	aB (3) aB	ab (2) aB
ab	AB (3) ab	Ab (2) ab	aB (2) ab	ab (1) ab

The numbers in parentheses are the numbers of phenotypes.

It is noteworthy that the regulatory genes sequentially exert their effects during the numerous developmental processes in an individual, depending on the time when and the tissue where they are expressed, that is to say, under the influence of the microenvironment of the cells. Information outside the cells is relayed through secretion and attachment of signalling molecules (for instance the fibroblast growth factors) to cell surface receptors and this determines the switching on and off of the expression of the genes within the cells. Thus, due to inductive interactions between cells originating from the embryonic epithelium and from the neural tube-derived mesenchymal tissues, genes turn on and off, depending on the stage of tooth development. In mice with a specific blocked-off gene (*MSX1* expressed in the dental mesenchyme), the expression of certain signals to the epithelium was inhibited, and not all the teeth developed. The importance of other genes has been established in the same way.[591] Up to a hundred genes and more are involved in the different stages of tooth development.[416] All these genes have a role in the mediation of cell communication, which occurs via small molecules to receptors and target genes.

To complicate matters, the external environment may modify the outcome of genetic regulation. The interaction between multiple genes and environmental factors results in complex diseases, such as type 1 diabetes mellitus. In this disease a familial clustering is assumed to involve at least 10 different genes, of which none is dominant.[544] References for this Introduction are included in the references for Chapter 1, beginning on page 293.

Section I
Developmental Anomalies

1 Anomalies of Number

1.1 Introduction

The human dentition may consist of fewer or more than the normal number of 20 deciduous or 32 permanent teeth. Fusion of two teeth may also give the impression of hypodontia (Section 1.2).

1.2 Hypodontia

Hypodontia is the term used for dentitions with fewer than the regular number of teeth due to *agenesis*, i.e. either absence of a tooth germ or failure of a tooth germ to develop. *Anodontia* is the congenital absence of all the teeth while the absence of many teeth is known as *oligodontia* or partial anodontia. *Isolated hypodontia* is the congenital absence of one or a few teeth. Incomplete dentitions not classified as having hypodontia by definition are those where teeth are absent due to failure of eruption, extraction due to caries or orthodontic treatment,[295] or where teeth have been lost due to trauma and other reasons.

Hypodontia is the most frequent of all congenital aberrations in humans, and also occurs in animals such as dogs.[245] The incidence of agenetic teeth in Caucasian populations seems to have increased during the twentieth century, but the available data are too limited to suggest a trend.[384]

The aetiology of hypodontia is not entirely clear, but genetic factors are most certainly involved. Because mutated genes associated with agenesis have developmental regulatory functions elsewhere in the embryo, associated defects in other tissues and organs are also possible.[591]

The skin develops from the ectoderm, one of the three primary germ layers, which is involved in the formation of the teeth. Patients with isolated dental agenesis may show unusual dermatoglyphic patterns of the palms of the hands and soles of the feet, suggesting a shared origin.[28] The combination of freckles, thin eyebrows and hypodontia[609] suggests the same. Therefore, isolated dental agenesis might be a minor manifestation of a systemic disorder.

1.2.1 *Isolated dental agenesis*

As mentioned above, isolated dental agenesis is the result of the absence of one or a few tooth germ(s). Missing teeth can lead to diastema (interdental spaces) in the dental arches. Displacement and tilting of the neighbouring teeth may close these spaces.

Epidemiology

Primary dentition

Less than 1% of children exhibit hypodontia in the deciduous dentition. The teeth most often involved are the maxillary incisors, followed by the mandibular central or lateral incisors,[112 134 220 372 394 445 469] and also the first molars.[112] When the deciduous canines are agenetic, [205 608] a syndrome (see Chapter 11) such as cleft lip is usually present.[464] Around 50% of children with hypodontia are missing one tooth, usually the maxillary lateral incisor; in the rest usually two or more teeth are missing.[134] Japanese children show agenesis more frequently (5%), which may represent an ethnic trait.[112 158]

Permanent dentition

Surveys, often retrospective, of some 160 000 children and adolescents from different countries and populations indicate that 2% to 10% of the permanent dentitions show isolated dental agenesis, third molars excepted.[1 10 31 47 55 89 94 112 129 131 159 169 170 208 210 219 231 268 279 294 352 362 371 374 388 410 414 421 423 441 469 485 488 508 541 594 595 629 638 648] One study found that 13% of orthodontic patients had hypodontia,[476] however, this sample is not representative of the population and the finding may be considered as an outlier.

The main body of data has been collected from European and American Caucasian populations, although

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some studies have included different ethnic and mixed populations. European and Australian children in general lack more teeth than North American Caucasians.[446] On average two teeth, frequently homologous teeth,[31] per individual are agenetic.[160]

Girls are significantly more susceptible to agenesis than boys,[1 31 47 169 200 219 279 476 485 488 452 566 664] but not all surveys have found a difference between the sexes.[159 374 497 501 574 665] Isolated dental agenesis may, however, occur about 1.4 times more often in girls than boys,[384 446] and agenesis of several teeth is also more common in girls.[210 585 595] In one study, the prevalence of hypodontia in Jewish children did not differ by sex, but girls lacked the maxillary lateral incisors more frequently and the boys the mandibular incisors.[170]

The overall prevalence of agenesis in the maxilla is comparable with that in the mandible, but there is a marked difference in the pattern of absence of tooth type between the jaws.[446] The five teeth most prone to agenesis in order of most to least prevalent, are: third molars > mandibular second premolars > maxillary lateral incisors > maxillary second premolars > mandibular lateral incisors.

However, other rank orders of agenesis of teeth, including teeth other than the ones mentioned above, have also been reported. Specific populations and inclusion of oligodont patients may account for the differences.[446]

Third molars Wisdom teeth are most often implicated in isolated dental agenesis, but the prevalence data vary. In 10–35% of adolescent and young adult dentitions, one to four third molars are absent.[5 33 34 73 129 200 231 234 250 260 255 276 308 412 441 455 511 535 554 594 596] In studies of third molar agenesis, subjects may not be very young since the teeth develop quite late in some individuals,[61 474] and older people may not recollect whether the teeth were extracted.

Third molar agenesis seems race-related.[33 132 260 524 554] For instance, 27% of the white population in the USA versus 2% of East Africans have missing wisdom teeth,[33] and more Chinese lack all four third molars than Caucasians.[132] Women lack wisdom teeth less often than men,[444] but some researchers did not find a sex difference.[346 354]

More so than other teeth, the third molars tends to show bilateral absence.[129 354 554] Almost 10% of subjects also lack other teeth when one or more third molars are agenetic.[73]

Mandibular second premolar Of the four frequently agenetic teeth (excluding third molars), 45% or more[47 466] are second mandibular premolars; they are bilaterally missing in almost half of the population missing these teeth.[574] The reported percentages for lower second premolar agenesis vary considerably, but may be as low as 3.5%. In some studies, the maxillary lateral incisors were the most frequently agenetic,[55 170 410 501 580 638] and in one study it was the mandibular lateral incisors.[131] Such variations in findings might be due to ethnic differences.[444 524] Studies in Caucasians are more likely to show absence of the mandibular second premolar (and maxillary lateral incisor), and Asian studies of the mandibular incisors. A difference between the sexes has not been established.[574]

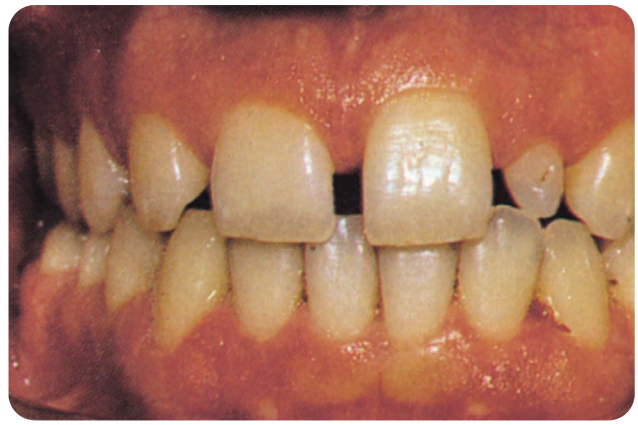

Figure 1.1 Agenetic right permanent maxillary lateral incisor; the contralateral tooth is underdeveloped.

Maxillary lateral incisor A quarter of the four most frequently agenetic teeth (excluding third molars) are the maxillary lateral incisors. In some studies these teeth are reported to be missing even more often than the second mandibular premolars. A meta-analysis showed almost equal rates of agenesis of the maxillary lateral incisors and the maxillary second premolars.[384] In about 2.2% of Caucasians and Israelis the maxillary lateral incisor is absent.[170 580] Bilateral agenesis is common,[446] and the anomaly may be more common in women.[566]

Figure 1.1 shows a congenitally missing right maxillary lateral incisor and an underdeveloped contralateral incisor, which is rarer than bilateral agenesia.[566] The reduced, often conical, morphology may represent an incomplete expression of agenesis.[444]

Maxillary second premolar This tooth accounts for some 20% of the four frequently agenetic teeth, excluding the third molars. The variations in figures may be ascribed to small sample sizes, but the large differences in reported prevalences is substantial and remains unexplained. Bilateral agenesis occurs thrice as often as unilateral agenesis.[444]

Mandibular central incisor In order of frequency of agenesis in the permanent teeth, the mandibular central incisors usually come last, but not in Chinese children in Hong Kong.[131] Occasionally, the lateral incisor has been found to be missing more often than the central. Figures 1.2 and 1.3 show two and four retained deciduous man-