ORIGINAL ARTICI

The genetics of human tooth agenesis: New discoveries for understanding dental anomalies

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The important role of genetics has been increasingly recognized in recent years with respect to the understanding of dental anomalies, such as tooth agenesis. The lack of any real insight into the cause of this condition has led us to use a human molecular genetics approach to identify the genes perturbing normal dental development. We are reporting a strategy that can be applied to investigate the underlying cause of human tooth agenesis. Starting with a single large family presenting a clearly recognizable and well-defined form of tooth agenesis, we have identified a defective gene that affects the formation of second premolars and third molars. With the use of "the family study" method, evidence is produced showing that other genetic defects also contribute to the wide range of phenotypic variability of tooth agenesis. Identification of genetic mutations in families with tooth agenesis or other dental anomalies will enable preclinical diagnosis and permit improved orthodontic treatment. (Am J Orthod Dentofacial Orthop 2000;117:650-6)

Agenesis of one or more teeth is the most common anomaly of dental development in man.[1] Several terms are being used in the literature to describe numeric dental anomalies. One of them, *oligodontia* literally means "few teeth." *Anodontia*, an extreme expression of oligodontia, denotes complete absence of teeth. The term *partial anodontia* is frequently used synonymously with oligodontia. *Hypodontia* is used to indicate a more complex entity, involving not only aberrations in number, size, and shape of the remaining teeth but also abnormalities in the overall rate of dental development and time of eruption.[2,3] The commonly used term *"congenitally" missing teeth* is a misnomer as permanent teeth that are most frequently missing are not present in the mouth at birth.[4] Tooth agenesis is a more informative term because it also implies the underlying developmental defect.

CLINICAL EPIDEMIOLOGY

Tooth agenesis limited to a few specific teeth occurs commonly and is often considered a normal variant.[5,6] Permanent dentition is more frequently affected than primary dentition. The incidence for permanent tooth agenesis ranges from 1.6% to 9.6% in the general population excluding third molars.[5,7-10] In the primary dentition, tooth agenesis is reported to be 0.5% to 0.9%.[11-13] Severe tooth agenesis (absence of 4 or more teeth other than third molars) has an estimated prevalence in the general population of 0.25%.[14]

The incidence of tooth agenesis varies with tooth class. Third molar agenesis is the most common with an incidence of 20% in population studies.[7,15] Opinions vary on the second most commonly missing tooth. Some investigators[16-20] believe that this is the maxillary lateral incisor, whereas others[8,21-23] believe that mandibular second premolar agenesis has a higher incidence. In a sample consisting of 5127 patients, agenesis of maxillary lateral incisors occurred with a frequency of 2.2% and agenesis of the second premolar with a frequency of 3.4%.[24] In reference to second premolars, agenesis of a single second premolar is the most common form and absence of the 3 premolars occurs least frequently.[25]

An interesting correlation on the number of missing teeth and the tooth class has been made by Muller et al,[17] based on a collection of 14,940 adolescents. They have noted that maxillary lateral incisors are the most frequently missing teeth when only 1 or 2 teeth are absent, whereas second premolars are the most frequently missing teeth when more than 2 teeth are absent.

Third molar agenesis has been associated with dental numeric and structural variations.[16,26,27] Bailit[28] has suggested that when a third molar is absent, agenesis of the remaining teeth is 13 times more likely.[28] Third molar agenesis also seems to predispose for reduced size[27,29-31] and delayed development[32,33] of certain

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teeth. According to Garn and Lewis,[34] if a third molar is absent, the molars and premolars of the same quadrant are delayed in formation and eruption. Third molar agenesis has also been linked to diminished stability of specific molar cuspal patterns.[27] Keene[27] was able to associate the reduction of the Carabelli cusp to third molar agenesis.[27] A relationship between absent teeth and the abnormal morphology of remaining teeth has been observed within other types of agenesis; agenesis of one lateral incisor is often accompanied by a small lateral on the contralateral side.[35,36]

Peck et al[37,38] have reported significantly elevated tooth agenesis frequencies in subjects with either maxillary canine-first premolar transposition, palatal displacement of the maxillary canine, or mandibular lateral incisor-canine transposition. Their observations point to a genetic model where disturbances in dental development and disturbances in the order of eruptive position are tightly associated.

Gender-preference has also been investigated as it relates to tooth agenesis. There are reports attributing higher incidence of tooth agenesis in women.[8,17,21] One study[39] has reported a female to male ratio of 3:2, although others[9] have been unable to confirm this finding.

Opinions vary in terms of the degree of symmetry presented in the dentition with tooth agenesis. According to Bailit,[28] most patterns are bilaterally symmetric, with the exception of maxillary lateral incisors where the left one is more frequently missing than the right one. Lundstrom[40] has observed that agenesis of teeth is often unilateral; approximately half the missing teeth are absent unilaterally.

The reported prevalence for missing teeth, excluding third molars, also depends on the population studied. In African Americans, agenesis has been estimated to be 7.7% with the mandibular second premolar most frequently missing.[41,42] Studies in Japan have demonstrated tooth agenesis in 9.2% of this population, mostly affecting the mandibular lateral incisor.[43] These reports suggest that there is a background-dependent variation to be considered in tooth agenesis.

Clinicians agree that tooth agenesis regardless of gender or race becomes more prominent in recent societies. It is not known whether this observation is an aberration related to better detection methods and patient's awareness or whether it is a real trend toward increased prevalence of dental abnormalities.

CLINICAL GENETICS

Monogenic Tooth Agenesis

Twin studies have been historically used to show the importance of the genetic component acting during tooth development to control both tooth size[44,45] and form.[46,47] However, there are reported cases[48,49] of monozygotic twins concordant for tooth agenesis, as well as cases[50-52] where variation in the expressivity is observed.

Population studies have shown that tooth agenesis can be manifested as an isolated finding or part of a syndrome.[42,53] Isolated forms may be sporadic or familial.[52] Familial tooth agenesis can be the result of a single dominant gene defect[8,35] a recessive[54] or X-linked.[55,56] Third molar agenesis cannot be explained in the majority of cases with a simple model of autosomal dominant transmission.[8] Speculations of a polygenic model of inheritance have also been reported in the literature.[57-60]

Grahnen[8] has suggested that tooth agenesis is typically transmitted as an autosomal dominant trait with incomplete penetrance and variable expressivity.[8] In Grahnen's sample, the penetrance was higher when the proband of the family had more than 6 missing teeth. Burzynski and Escobar[61] calculated the penetrance of numeric anomalies of dentition to be 86% with the use of Grahnen's data. Woolf[62] has suggested that in families exhibiting dominant inheritance of incisor agenesis, the responsible gene tends to show reduced penetrance and variable expressivity.[62] Peg lateral incisors or rudimentary third molars may reflect incomplete expression of a gene defect that causes tooth agenesis; unilateral agenesis may be a result of reduced penetrance.[25]

Inherited Syndromes Associated with Tooth Agenesis

More than 60 syndromes categorized in On-line Mendelian Inheritance in Man (OMIM) are associated with tooth anomalies, implying that common molecular mechanisms are responsible for tooth and other organ development.[63,64] Agenesis of numerous teeth is commonly associated with specific syndromes or systematic abnormalities and particularly related to ectodermal dysplasia.[5,65]

In addition to inherited defects, somatic diseases such as syphilis, scarlet fever, rickets, or nutritional disturbances during pregnancy or infancy can affect tooth and other organ development, thereby, leading to tooth agenesis in association with other anomalies. Further, cranial irradiation early in development can produce glandular dysfunction as well as dental anomalies.[66,67]

DENTAL EVOLUTION

Dental anthropology has been an active area of research investigating the evolutionary aspects of tooth development. Variations in the number, size, and morphology of teeth among and within populations have provided insights into the genetic basis of odontogenesis.

Teeth probably originated as dermal structures called "odontodes," which subsequently migrated into the mouth, where they became associated with bones.[68]

Initially, teeth were identical conical spacially separated dental units (homodonty). Heterodonty, the divergent morphology of teeth in the dentition, has evolved from homodonty in a number of species, particularly mammals.[69] The fundamentals of comparative odontology have been recognized more than 2000 years ago by Aristotle.[68] Teeth are vertebrate-specific and within vertebrates, species-specific. Tooth shape varies with position in the jaws and is bilateral and symmetric.

Phylogenic changes in the dentition correlate with functional adaptation.[70] Teeth and teeth-bearing bones evolve together.[69] The reduction in tooth number is concomitant with the reduction in the size of the jaws in human evolution and is believed to be a continuing evolutionary trend. Lavelle et al[15,71] studied monkeys, apes, great apes, and homo sapiens, and have noted that homo sapiens have developed a tendancy toward a shortened maxillomandibular skeleton compared to their ancestors. The number of teeth diminishes in parallel with these changes in the jaw skeleton.[67] It has been suggested that one incisor, one canine, one premolar, and two molars per quadrant is likely to be the dental profile of future man.[5,72]

THEORIES ABOUT TOOTH AGENESIS

Developmental defects of teeth have always been very intriguing. Attempts were made to explain them with evolutionary and anatomic models such as Butler's field theory, odontogenic polarity, or Sofaer's model of compensatory tooth size interactions.

Butler's theory (1939) attempts to explain why certain teeth fail to form more than others. According to this hypothesis, mammalian dentition can be divided into 3 morphologic fields corresponding to incisors, canines, and premolars/molars. Within each field, one "key" tooth is presumed to be stable; flanking teeth within the field become progressively less stable. Considering each quadrant separately, the key tooth in the molar/premolar field would be the first molar. This schema positions the second and third molars at the distal end of the field, and the first and second premolars on its mesial end. Based on Butler's theory, the third molar and the first premolar would be predicted to be most variable in size and shape. Clinical epidemiology supports this view for the third molar, but not for the first premolar. However, the earliest mammals had 4 premolars, whereas some higher primates, including man, have lost the first 2. These lost teeth would have been farthest from the key tooth and in an evolutionary sense could be considered unstable.[28]

Clayton[7] observed that the terminal or most posterior tooth of a tooth series (incisors, premolars, and molars) was missing most frequently in a sample of 3557 human subjects. He hypothesized that the teeth most often missing were "vestigial organs" with little practical value for modern man. In the evolutionary process, these teeth provide no selective advantage for the species and hence have been lost.[67]

Sofaer et al[73] have challenged the association between absent teeth and those reduced in size. Variation in expression and penetrance of tooth agenesis is predicted to be a compensatory interaction between tooth germs during development. In a study of Hawaiian children, they noted that if the central incisor is large then the adjacent lateral incisor tends to be absent. However, if the lateral incisor is peg-shaped, the adjacent central incisor tends to be present, but relatively small. They speculated that agenesis occurs when there is insufficient primordia for tooth germ initiation, whereas peg-shaped laterals occur when there is sufficient primordia but a poor environment. Lateral incisors develop after the centrals and their initiation depends on the availability of the necessary local requirements.[28] Absence or reduction in size of the teeth on one side induces a compensatory increase in size of the teeth of the contralateral side.

Svinhufvud et al[74] have explained the selectivity of tooth agenesis in terms of an anatomic rather than an evolutionary model. These researchers suggested that certain regions during tooth development (eg, areas of embryonic fusion) are more susceptible to epigenetic influences and hence agenesis. For example, the most frequently missing or variably sized tooth in the maxilla, the upper lateral incisor, develops in the area of the embryonic fusion between the lateral maxillary and medial nasal processes. In the mandible, permanent tooth agenesis occurs most frequently in the area of the second premolar. This corresponds to the distal end of the primary dental lamina, and because of its susceptibility to agenesis, this area is called a "fragile" site.[25] Interestingly, however, this site of mandibular agenesis appears specific for permanent dentition; the loss of second primary molars is rare.[25] A third site where tooth agenesis occurs frequently is the area where the 2 lower central incisors develop. Here, the fusion of the 2 mandibular processes is required to form the midline of the future mandible. This midline region is likely to be another fragile site.

Kjaer[75] has explained the location of tooth agenesis by neural developmental fields in the jaws (incisor field, canine/premolar, and molar field). The region within a single field where innervation occurs last is more likely to manifest tooth agenesis.

Normal tooth development seems particularly sensitive to defects in craniofacial development.[76] Disturbances of the embryonic jaw mesenchyme are often revealed predominantly by their effects on the teeth.

Early craniofacial defects, which could result in jaw abnormalities, are often masked by bone remodeling, and therefore, tooth agenesis may actually serve as a better indicator of developmental jaw defects.

ODONTOGENESIS: AN APPEALING AREA OF RESEARCH

Because of their unique features, teeth have become very appealing for studying. The term *odontogenesis* has been initially used to describe events related to the origins and initiation of tooth formation. ten Cate[77] has expanded this definition even further so that it also includes the origins and formation of tooth-supporting tissues, namely cementum, periodontal ligament, and alveolar bone, all tissues of dental descent. Experimental investigation of odontogenesis started over 60 years ago. Before that time, our understanding of tooth development consisted mainly of descriptive dental histology.[77] A lot of information on tooth formation has been accumulated recently.[77-81]

However, these studies were not focused on human beings and the molecular basis of human tooth development remains largely undefined. One approach to improve our understanding of both normal and abnormal odontogenesis is by identification of human mutations that cause dental anomalies. Investigation of the underlying cause of inherited dental anomalies could reveal how the tooth-forming processes are perturbed and would eventually give us a better understanding of normal odontogenesis.

HUMAN MOLECULAR GENETICS: A NEW APPROACH

Identification of the underlying cause of a condition starts with the localization of its defective gene in the human genome. Before 1980, methods to establish the relationships between inherited conditions and the molecular genetics responsible for these conditions were not well established. The discovery of genetic markers across the human genome, the development of sophisticated statistical methods to analyze the cosegregation of markers and diseases, and the innovations in DNA cloning and sequencing have made it possible to link a stretch of DNA with a particular inherited phenotype.[82] Advances made by the human genome project (HGP) over the past several years have greatly enhanced the feasibility of mapping inherited conditions, such as familial tooth agenesis (FTA).

FTA is a clearly recognizable, well-defined, relatively common dental anomaly and therefore, a good example for application of human molecular genetics methods. The first step in this approach involves identification and clinical characterization of families presenting tooth agenesis. Important features in family selection are pedigree size and structure. The family should be big with a minimal number of deceased individuals and large numbers of siblings that render the meioses more informative. Knowledge of the genetic model (ie, mode of inheritance of the condition) and diagnostic certainty are paramount.

Tooth agenesis may involve a disparate group of findings. Even within the familial tooth agenesis cases that are transmitted as autosomal dominant traits, there is clinical evidence for significant variability. This suggests that a multiplicity of gene defects may cause FTA and thus, single large families are preferable to groups of small families for these studies.

A large family and an accurate assessment of the phenotype (ie, diagnosis) are the basis to perform genetic linkage studies. It is via genetic linkage that the chromosomal location of a defective gene can be identified. The objective of these studies is to determine whether two genetic traits are segregating independently—according to Mendel's laws—or are cosegregating within a kindred because of their close physical proximity. These two genetic traits are a genetic marker (DNA polymorphism of known chromosomal location) and the condition of interest (eg, familial tooth agenesis). Genes located close to each other (physical proximity) are passed together from parent to child.[82] Therefore, cosegregation of a phenotype such as tooth agenesis and a particular known marker would suggest that these genetic traits lie close to each other, on the same region of a chromosome, providing at the same time, the locus for the defective dental gene.

Once the condition locus is identified in one family the following step is designed to determine whether the same chromosomal location is responsible for tooth agenesis in other families. In genetic terms, such search addresses the question of whether FTA is genetically heterogeneous. This could reflect the possibility of either different mutations in the same gene or that more than one mutated gene (potentially on different chromosomes) cause similar phenotypes. Recognition of genetic heterogeneity is important because it points to the identification of other genes that may participate or independently yield to a similar phenotype. Subsequent refinement of the condition locus leads to the identification of specific genes and the mutations that produce the condition.

Using this strategy[83] in a family presenting autosomal dominant agenesis of second premolars and third molars (Fig 1), we were able to find out in which chromosome the abnormal dental gene was located, what this gene was, and what in the gene causes this abnormality. In particular, we identified a location on chromosome 4p where the gene that is responsible for tooth

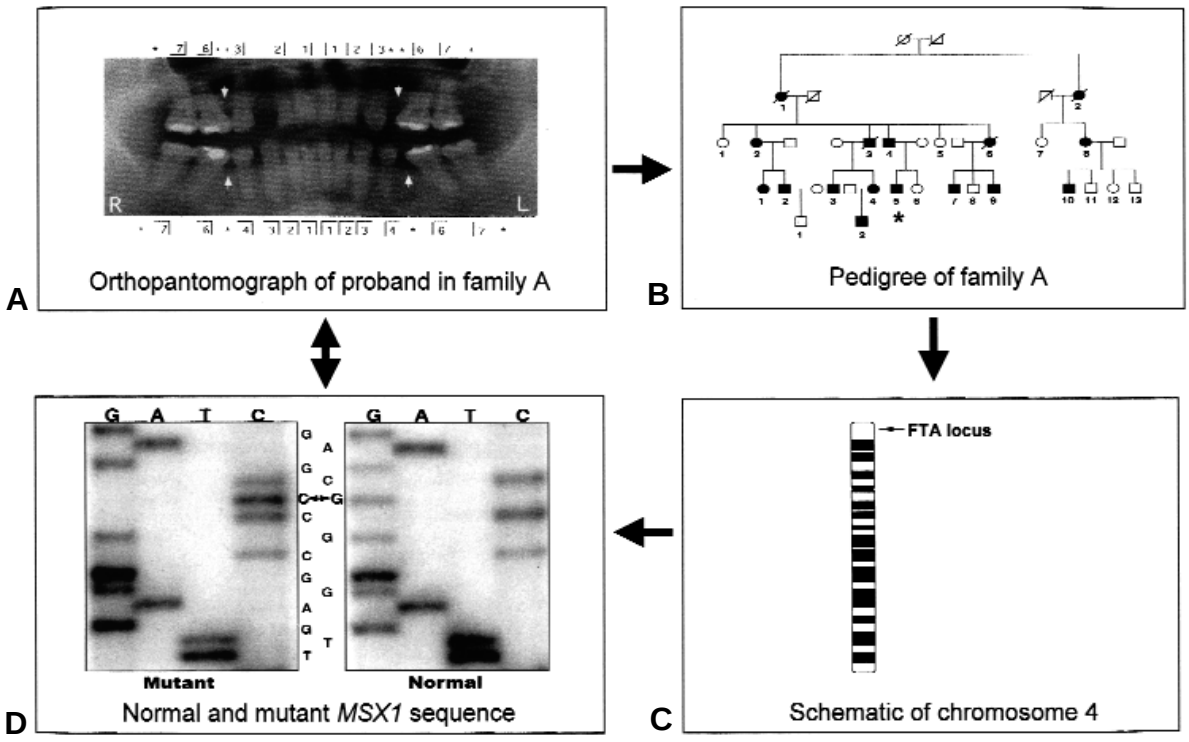

Fig 1. Steps in studying the molecular basis of tooth agenesis: Diagnosis of tooth agenesis in an individual (index case or proband) (**A**) was followed by recording of the dental history of his family and construction of the pedigree (**B**; proband at asterisk). Advances in the Human Genome Project (eg, genetic linkage studies, gene cloning and sequencing) enabled us to initially localize the defective gene in the short arm of chromosome 4 (**C**) and subsequently (**D**) to dissect the exact genetic mistake (point mutation in the *MSX1* gene) that led to tooth agenesis in family A. (Reproduced with permission from Nature Genetics)

agenesis in this family resides. Subsequently, we discovered the culprit gene by detecting a point mutation in the *MSX1* gene of all affected family members.[83]

Given the diversity in the number and the location of missing teeth observed between families, we have hypothesized that the differences in the clinical expression of FTA reflect genetic variability in the population. To test this hypothesis, 5 additional families presenting different types of missing teeth were evaluated. We determined that defects in multiple genes contribute to the interfamilial clinical variation of tooth agenesis.[84,85]

This article aims to encourage orthodontists to extensively inquire about the family history of individuals with dental anomalies. Observations of familial patterns, collection of clinical data combined with molecular genetics expertise may bring about tremendous gains toward the understanding of the genetic roots of tooth anomalies. Collaboration between clinicians and researchers is absolutely essential for this type of genetic studies.

Identification of the tooth agenesis-causing genes can provide considerable information not only about this dental defect but also about the physiologic processes perturbed by the mutations. Definition of the genetic event that causes familial tooth agenesis should also lead to a better understanding of the events that cause nonheritable dental anomalies. Identification of mutated genes that cause FTA will enable studies to assess the mechanism by which environmental factors modify gene expression and result in similar clinical phenotypes. It is also envisaged that identification of the FTA genetic defects will enable studies to determine whether nonsyndromic and syndromic tooth agenesis have similar causes. Though the FTA form of tooth agenesis associated with this mutation is relatively rare, analyses of the function of this gene in the development of the condition could help in understanding the more common forms.

Ultimately, elucidation of the pathogenic mechanism in FTA will provide insights into the role of teeth

in craniofacial development and will advance understanding of cranio-orofacial dysmorphology. Knowledge gained from normal and abnormal development can be useful toward advancing diagnosis, treatment prognosis, and prevention of congenital malformations.

CONCLUSIONS

We have presented a human molecular genetics approach to odontogenesis and have established the first genetic residence for FTA. With the use of methods of positional cloning, a defective molecule determining second premolar and third molar formation was identified. We have also provided evidence that FTA is genetically heterogeneous suggesting that more than one gene defect contributes to the clinical variability of this dental condition. Tooth development is a very complex process and involves many "players." The *MSX1* gene is just one of them. We therefore, have a long way to go until we reach our goal, which is the understanding of odontogenesis. Clinical dentistry is being reformed following the demands of the 21st century. Understanding of human dento-orofacial genetics and their impact on diagnosis, prevention, and eventually therapeutics are becoming integral parts of health care.[86]

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