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Genes Underlying Familial Hypodontia: A Review and Discussion of the Role of Dental Hygienists in Future Research

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Congenitally missing teeth, or hypodontia, is one of the most common abnormalities of the human dentition and has a critical and often lifelong impact on the oral health of affected individuals. Here we review hypodontia and describe the patterns of inheritance it can display. A short review of tooth development and a primer in human genetics are presented. Approaches used to determine the underlying cause for various forms of hypodontia are discussed and information about genes discovered to date is reviewed. The role that the dental hygienists can play in facilitating the discovery of novel genes for hypodontia is illustrated.

Keywords: Hypodontia, missing teeth, families, inheritance, genes

Introduction

Having healthy and normal dentition is crucial to one's well-being. Teeth are necessary for tasting, chewing, and swallowing food. Teeth are integral in the balance of the orofacial complex and are also important for clearly discernible speech and for proper smiling and kissing. Ultimately, these attributes contribute to facial aesthetics and, as a direct consequence, to one's emotions, appearance, and self-esteem. The importance of a healthy mouth and teeth is most apparent when an individual encounters problems such as a toothache, bad breath, or missing teeth. These dental problems may trigger feelings ranging from anxiety or embarrassment to severe pain and dysfunction. Congenital lack of teeth is a condition that can seriously compromise the oral health of the affected individual. Dental hygienists have a very important role in detecting, treating, and explaining to the family the implications of congenitally missing teeth. The purpose of this article is to provide dental hygienists with a primer in human genetics, a general review about familial hypodontia, patterns of inheritance, and the technologies that are used to detect the molecular causes of this disorder. Dental hygienists have the potential to become important referral sources to geneticists interested in determining the cause of familial hypodontia. This article also highlights the need for dental hygiene education to include the genetic content necessary to keep pace with this burgeoning area of research and dental hygienists' potentially important role therein.

Overview of Teeth Development

Tooth development results from the interaction of epithelial and mesenchymal cells in the human embryo, which ultimately results in 20 primary and 32 permanent teeth. This physiological process includes initiation, proliferation, differentiation,

morphogenesis, and maturation. After initiation (sixth week), tooth development proceeds through the basic stages: bud (eighth week), cap (ninth to 10th week), and bell (11th to 12th week), where precise and intricate interaction of a multitude of proteins directs the development of the different types of teeth.

Figure 1 shows the stages in tooth development and the many growth factors and transcription factors that have been implicated in the process through studies in mice. At the initiation stage, around the sixth week of human development, the oral ectoderm gives rise to the oral epithelium, and then to the dental lamina adjacent to the deeper mesenchyme separated by a basement membrane. Around the eighth week, the bud stage occurs, which is characterized by the rapid proliferation of the dental lamina that penetrates the mesenchyme. These structures will develop into the tooth germ and its associated supporting tissues. The cap stage occurs between the ninth and 10th week of human prenatal development. The proliferation continues, but the tooth bud does not grow anymore. Instead, there is an unequal growth in different parts of the bud, giving rise to a cap shape attached to the dental lamina. The tooth germ, composed of the enamel organ, dental papilla, and dental sac, is formed at this point. At the bell stage, differentiation at all levels occurs to its furthest extent, and the cap shape of the enamel organ assumes a bell shape. The final stages (differentiation) of odontogenesis include apposition, during which the enamel, dentin, and cementum are secreted as a matrix. The matrix is partially calcified and serves as a framework for later calcification and maturation, which is reached when the dental tissues are subsequently fully mineralized.[1,2,3]

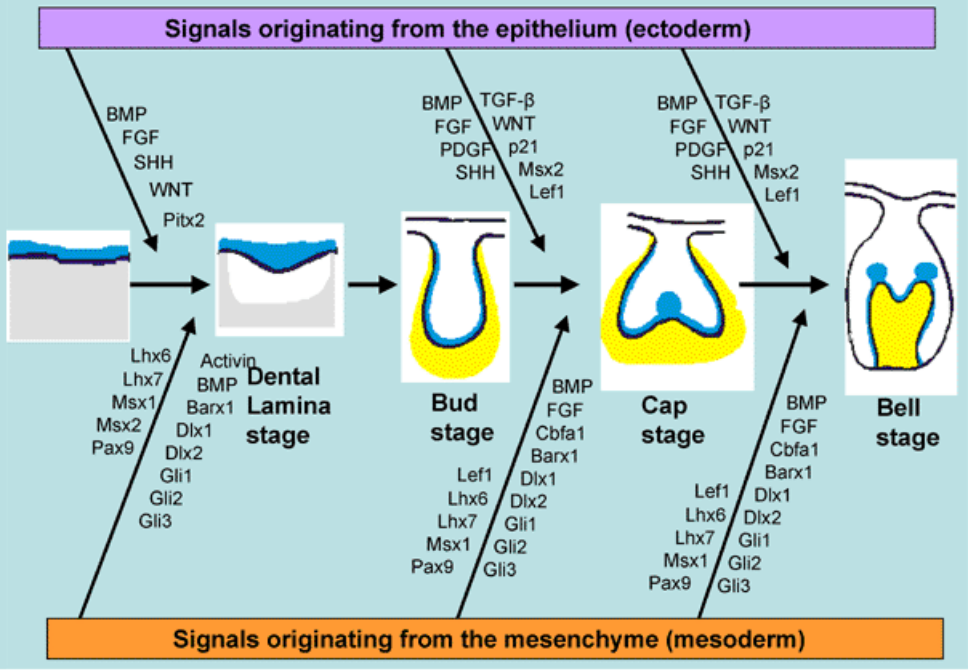

Figure 1. Schematic diagram showing the different stages in tooth development and the many growth factors and transcription factors that have been implicated in the process through studies in mice. Growth factors are shown in capital letters and transcription factors are shown in lower-case type.

Tooth Agenesis: Definition and Characteristics

Tooth agenesis can occur in association with syndromes, often involving multiple organ systems such as ectodermal dysplasia,[4] or it can occur as an isolated condition when it is referred to as non-syndromic hypodontia. The absence of teeth is broadly referred to as hypodontia, with some authors drawing a distinction between the congenital absence of one to six teeth (excluding third molars) as hypodontia, and the absence of more than six teeth (excluding third molars) as oligodontia. Anodontia refers to the complete absence of teeth.[5,6]

The agenesis of third molars occurs in approximately 25% of the population. Mandibular second premolars are missing twice as often (5%) as the mandibular second premolars (2.5%). The maxillary lateral incisors are absent in about 2.5% of the population, whereas the mandibular central incisors are absent in less than 1%.[7] The agenesis of canines is very infrequent, as is that of maxillary central incisors, which are commonly absent in Axelfeld-Rieger syndrome, characterized by specific anomalies, both ocular (such as iris hypoplasia, iridocorneal adhesions, and microcornea with opacity) and dental (ranging from small teeth to partial or complete hypodontia).[8]

Some relationship exists between malpositioning of permanent canines and hypodontia. Several studies indicate a significantly elevated prevalence rate for tooth agenesis in association with a palatally displaced canine.[9] The palatally displaced canine (PDC) and mandibular lateral incisor-canine malposition (Mn.12.C) appears to be associated with agenesis of third molars, and maxillary canine-first premolar transposition (Mx.C.PI) appears to be associated with elevated maxillary incisor agenesis.[10]

Human Genetics: A Primer

The human body is made up of 1013 cells, each of which contains the same genetic instructions that specify the information needed to build and maintain the individual. This complete set of instructions comprises the human genome. The genome consists of DNA that is organized into compact structures called chromosomes within the nucleus of each cell. Each chromosome consists of two long DNA strands twisted around each other. Four repeating building blocks (nucleotides), namely A, C, G, and T, constitute the backbone of each DNA strand. DNA sequence refers to the order of these four nucleotides, and it is the particular order of nucleotides in each person that determines their unique characteristics. A gene is a stretch of DNA sequence on a chromosome that specifies the information needed to encode a specific protein. The human genome is currently thought to encode 20,000 to 25,000 genes. Proteins play a key role in the structure and function of a cell. Each tissue in the human body, while having the same exact DNA, has a unique set of proteins, as different genes are active in different cell types, depending on the specific function of the cell.

The DNA within the nucleus of humans is organized into 46 chromosomes that comprise of two sets of chromosomes, one inherited from the father and the other inherited from the mother. There are 23 chromosomes in each set: 22 autosomes and a sex chromosome (either an X or a Y chromosome). Males have 22 pairs of autosomes and an X and a Y chromosome, while females have 22 pairs of autosomes and two X chromosomes.

Some human anomalies are caused by defects in chromosomes that can actually be visualized under a microscope, such as an extra copy of chromosome 21 in Down's syndrome or a deletion of a large segment of chromosome 17 in Smith-Magenis syndrome. However, the vast majority of human diseases are caused by very subtle changes in DNA called mutations. The most common type of DNA mutation is a single nucleotide change. For example, a change from an A to a G in the DNA sequence results in an altered protein whose function is either compromised or completely lost. The vast majority of mutations in DNA are, however, silent, with no phenotypic consequence. Other types of mutations include deletion or addition of one or more nucleotides in the DNA sequence.

Mutations can be either inherited from a parent or acquired during an individual's lifetime. In the former case, the mutation is present in all cells of the body, while in the latter case, it could be restricted to a particular part of the body, depending upon the stage of the life in which the mutation was acquired. Most mutations are repaired using enzymes whose role is to edit the DNA while the cell is dividing; but, as people age, the repair machinery can become inefficient. The cell has an elaborate repair system to prevent mutations from occurring when the cell is dividing by "proofreading" the DNA while it is replicating, but this system can go awry occasionally, especially as humans age. In addition, environmental agents such as radiation or toxic chemicals can damage DNA, thus introducing mutations.

Inherited human diseases can pass through families in a dominant, recessive, or complex mode (Figure 2). A dominant disease results if one copy of the two copies of a given gene is defective. Examples of inherited dominant diseases include achondroplasia (or short-limb dwarfism), myotonic dystrophy, and Huntington's disease. Even though one copy of the gene is normal, the abnormal copy of the gene is able to override it, causing disease. Dominant diseases can be traced

through family pedigrees and appear to spread vertically because everyone carrying a dominant mutant allele (form of the gene) generally shows the disease symptoms.

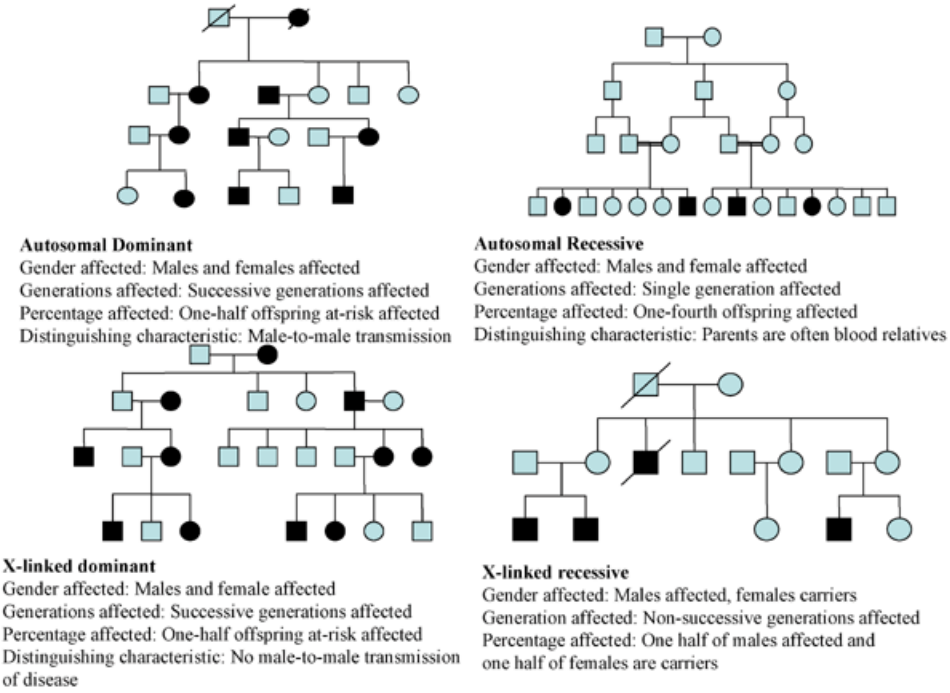

Figure 2. Sample pedigrees showing various patterns of Mendelian inheritance of a disease. Squares = males, circles = females, affected individuals = filled symbols, diagonal line = deceased individual.

Recessive inheritance means that two abnormal copies of the gene must be present for the individual to be affected. Cystic fibrosis, a disease in which breathing and digestion are impaired, is an example of a recessive disease. Tay-Sach disease, which is common in people of Ashkenazi Jewish origin, is another recessive disease. In a recessive disease, both copies of the gene must be mutated to produce the disease. Parents of the affected individual show no symptoms even though they carry one mutant copy of the gene. If both parents are carriers of the gene, the child has a one in four chance of receiving a recessive allele from each parent and inheriting the disease.

When the mutation in a gene underlying a disease that is located on the X-chromosome is dominant, both males and females are affected, although the females are usually less severely affected. This is because females have two X chromosomes and, during development, one of the two X-chromosomes is selected at random and inactivated to allow X-chromosome gene dosage between males and females to be balanced. Thus, in some cells of the body, the X-chromosome carrying the disease allele is inactivated and, in others, the "normal" X-chromosome is inactivated. An example of an X-linked dominant disease is hypophosphatemia. If the mutation on the X-chromosome is recessive, males are affected and females are typically carriers with no symptoms or very mild symptoms. An example of such a disease is hemophilia.

Diseases associated with mutations in multiple genes and whose phenotypes can be influenced by non-genetic factors, such as environmental influences, display a complex inheritance pattern. Figure 1 shows the different modes of Mendelian inheritance and their particular characteristics.

Etiology and Inheritance

Non-syndromic hypodontia can be caused by environmental and/or genetic factors. Environmental factors that can arrest tooth development include trauma, chemotherapy, systemic diseases, or endocrine disturbances.[11] Mutation of one or more genes can also cause hypodontia and often results in the prevalence of hypodontia among several members of the same

family in multiple generations. Familial hypodontia can display several different patterns of inheritance. These can be autosomal or X-linked dominant or recessive patterns, or polygenic inheritance patterns.[12]

Molecular Approaches

If genetic factors are assumed to cause hypodontia, there are two basic approaches used to identify the causative gene: functional and positional cloning. In functional cloning, the identification of the gene is based on knowledge of the specific biochemical defect in the disease, which is then used to clone the gene encoding the protein. For instance, it was long known that patients with phenylketoneuria (PKU) were deficient in phenylalanine hydroxylase (PH). Antibodies to PH were used to clone the corresponding gene. If, however, only the phenotype of the disease is known, with no clues to the underlying biochemical defect, the gene has to be sought on the basis of its chromosomal location. This method is called positional cloning and is done by linkage analysis, which is based on the segregation of genetic markers with the disease in families.[13]

Gene Mapping by Linkage Analysis

Positional cloning refers to the process in which the gene underlying the disorder is localized and identified in the genome, beginning with comparison of the inheritance of the disease and genetic marker loci in affected families. Success of gene identification by this method has four requisites: (1) large families with several affected individuals; (2) an accurate diagnostic test enabling clear distinction of affected and unaffected individuals; (3) a defined Mendelian pattern of inheritance; and (4) polymorphic DNA markers. A genetic marker is a segment of DNA with an identifiable physical location (locus) on a chromosome whose inheritance can be followed because it is "polymorphic." A polymorphism is a variation in DNA sequence that is seen in at least 1% of chromosomes within a population, and it allows distinction of the maternal and paternal chromosomes of an individual. Microsatellites are short tandem repeat markers with a high rate of polymorphism and dense distribution throughout the genome. These short sequences of DNA are used as gene markers to track inheritance in families. These markers, combined with the polymerase chain reaction (PCR) technique, can detect length of polymorphisms in microsatellite regions that can be traced in several generations.[16]

Because DNA segments that lie near each other on a chromosome tend to be inherited together, markers are often used as indirect ways of tracking the inheritance pattern of a gene that has not yet been identified. The first step is to define the clinical features, or phenotype, and to examine how the absence of teeth segregates within the family, thereby establishing the pattern of Mendelian inheritance for the trait. Markers spanning the genome and spaced at regular intervals, and the segregation of those markers in relation to the disease, determine the genotype of the families. If the marker and the disease loci are close enough, they will tend to segregate together.[14] This segregation happens more often than expected by chance. The association of genes and/or markers that lie near each other on a chromosome is termed "linkage." Linkage analysis is the method most often used in mapping studies (Figure 3). In linkage analysis, the co-segregation of the prospective gene that causes hypodontia and genetic markers in a family are followed and measured. If two loci are close to each other on the same chromosome, the chance of recombination between them is low and they are linked. Statistical analysis is necessary to calculate the probability of linkage in a pedigree.[15]

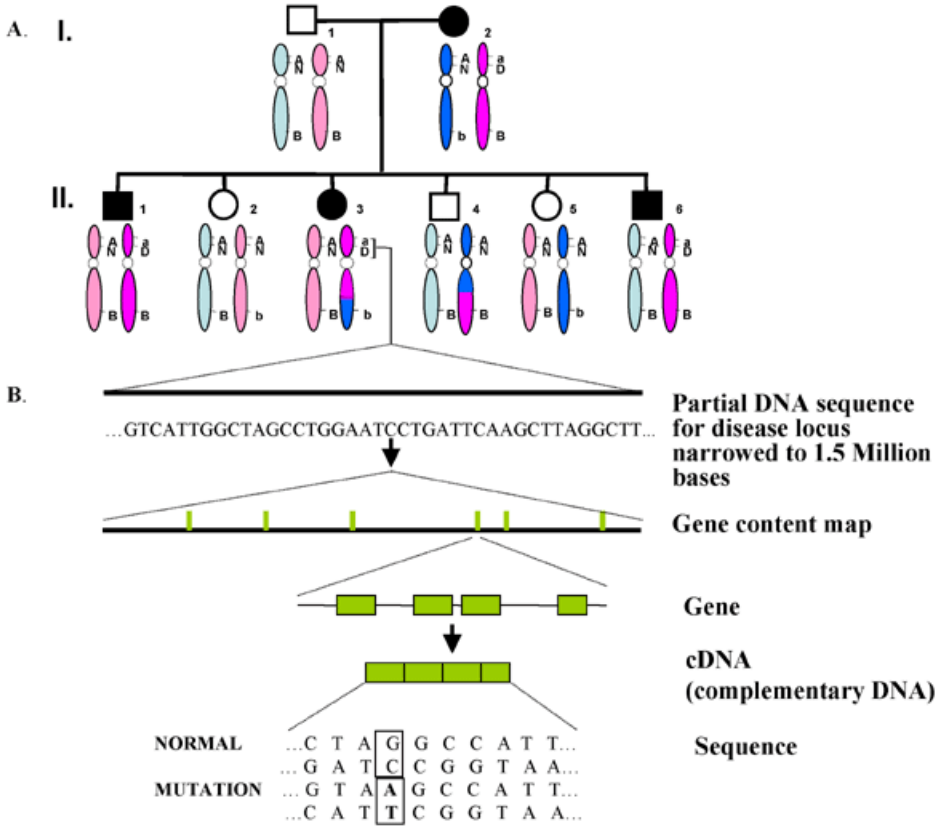

Figure 3. Schematic diagram of positional cloning of a disease gene by linkage analysis.

(A) The gene is initially mapped to a particular chromosomal region by linkage analysis which tracks the segregation pattern of marker loci and the disease within members of a given kindred. Symbols are as described in Figure 2. The segregation pattern of allele systems A/a and B/b at the marler loci on the short arm and the long arm of a hypothetical chromosome, respectively, indicates that the disease allele D segregates with the allele a but shows random segregation with alleles B or b due to recombination.

(B) Fine mapping and identification of the disease gene. The overall strategy used to identify the mutation within a candidate gene is shown, beginning with the DNA sequence of the large region, narrowed by linkage analysis obtained from public databases, to the identification of a single base change leading to the disease.

Genes Associated with Hypodontia

The morphogenesis of the teeth, like the development of the whole embryo, is under strict genetic control. More than 200 genes have been demonstrated to participate in tooth formation, including genes encoding growth factors, second messengers, and transcription factors.[17,18 19] Experiments with mice have demonstrated that deficient function of several transcription factors that are part of the signaling network results in arrested tooth morphogenesis.[20,21,22]

In recent years, three specific sites in the genome have been associated with hypodontia. Absence of second premolars and third molars is associated with mutations in a protein called MSX1.[23] Mutations in PAX9, another transcription factor, cause oligodontia involving molar teeth.[24] The absence of multiple permanent teeth in a large Chinese kindred has been mapped to a chromosome 10q11.2 with the gene yet to be identified.[25]

Some genes play a critical role in cell differentiation during the early stages of embryogenesis. Expression of these genes like Msx1 has been strongly implicated as crucial to the normal development of various craniofacial structures.[26,27] Msx1, a transcription factor, is strongly expressed in the dental mesenchyme and excluded from the dental epithelium throughout the bud, cap, and bell stages of dental development.[28] The role of Msx1 function is evidenced in the mice lacking this gene, which manifest a secondary cleft palate, deficiency of the alveolar complex of the mandible and maxilla, and failure of tooth development.[29] Msx1 plays a critical role in mediating epithelial-mesenchymal interactions during craniofacial bone and tooth development.[29,30] Several mutations in Msx1 have been reported in familial hypodontia, including missense mutations[31] and mutations that cause a truncated dysfunctional MSX1 protein.[32] Despite information of the regulation of Msx1 gene expression, the target genes controlled by Msx1 during organ formation remain unknown.

Pax9 is a member of a family of transcription factors that play a key role in development. The complex expression pattern of Pax9 during mouse development suggests that it plays a crucial role in the development of several organs. Complete absence of the Pax9 protein in mice causes arrested development of teeth at the bud stage and malformations of the palate, thymus, and parathyroid glands, among other malformations.[33] Several investigators, including those in the authors' laboratory, have demonstrated a direct relationship between mutations within these genes and familial hypodontia.[34] Different kinds of mutations, including loss of the entire Pax9, gene have been identified[35,36,37] in hypodontia families.[38]

The Role of the Dental Hygienist

Congenitally missing teeth, whether they are isolated conditions or associated with a syndrome, can affect the oral and overall health of individuals. Depending on the severity of the hypodontia, individuals with missing teeth may make nutritional choices based on comfort and ease of ingestion, rather than based on nutritive value of foods. Thus, affected individuals may choose soft foods and avoid fresh fruits and vegetables, which could have an adverse effect on the overall health of the individual. Dental hygienists should be aware of these effects and discuss them with primary care dentists and patients as appropriate.

The impact of congenitally missing permanent teeth on the developing dentition can be significant. When treating patients, many factors need to be taken into consideration including, but not limited to, aesthetics, patient age, and growth potential, as well as periodontal and oral surgical needs. If, by casual conversation, a dental hygienist learns that a patient has a family history of the condition, he or she needs to inform the dentist in order to evaluate both immediate and long-term management of the patient's oral care. An appropriately trained and/or experienced dentist should manage the patient, and a team approach may be needed.

The goal of the Human Genome Project was to determine the DNA sequence of the entire human genome and to map all the genes in the human genome, which will ultimately allow one to ascribe a function to these genes in normal human development and in disease. The completion of the Human Genome Project in March 2003 has made available almost the entire DNA sequence of all 24 human chromosomes. DNA sequence of the mouse, rat, and other model organisms has followed in rapid progression, and this explosion of genomic information has opened the door to the identification of the genetic etiology of various inherited disorders at a very rapid pace. With the addition of more polymorphic markers throughout the entire genome, better and more cost- and time-effective approaches will be available to tackle Mendelian and complex human diseases, including familial hypodontia. The discovery of new genes important for human tooth development will enable us to develop a complete picture of all the factors necessary for the formation of a specific tooth, which will have applications in the treatment of both inherited and acquired tooth agenesis. However, these advances will have no meaning if the rare families affected with hypodontia and other dental anomalies remain anonymous. The role of the dental hygienist in identifying patients with this problem cannot be over-emphasized.

Dental hygienists can be important facilitators for the molecular geneticist, as they have regular contact with a wide range of patients who seek routine or specialized dental care. In contrast to general dentists or orthodontists, dental hygienists spend more time with the patient, which may provide opportunities to determine if the hypodontia is likely familial. Thorough exploration, dental hygienists may help identify the relationship of an individual patient's hypodontia to the

same condition presenting in other family members. Dental hygienists are in a unique position to refer the patient to a molecular geneticist in order to facilitate gene identification.

Thus, dental hygienists are not only promoters of oral health, but are also referral sources for persons with familial hypodontia, explaining to them the importance of participating in research studies that ultimately benefit the whole population.

Those wishing to participate as a collaborator in a familial non-syndromic hypodontia project, or other projects, are invited to please contact the principal investigator, whose laboratory is focused on determining the causes of various inherited dental abnormalities.

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Notes

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