16

Congenital Genetic Disorders and Syndromes

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OUTLINE

Our understanding of genetics and the genetic basis of disease has increased dramatically over the last 20 years. During this time, scientists have ascertained the sequence of the entire human genome (more than 3 billion nucleotides of DNA) and have discovered new ways that diseases and disease susceptibility are inherited.

As health care professionals, we have gained information from the Human Genome Project that provides us with many opportunities as well as challenges. This information has given us the ability to understand diseases at a molecular level. In addition, diseases that were once thought to be influenced primarily by environmental factors are now known to have genetic factors that modulate their severity. More recently, gene-environment interactions and epigenetics have been shown to contribute to disease susceptibility. Access to the sequence of the entire human genome will continue to facilitate the identification of additional disease genes and allow us to understand the complex interactions that occur between genes and regulatory proteins. The ability to identify single-nucleotide changes (referred to as polymorphisms) will help us understand individual risk factors for disease and how to tailor prevention and treatment strategies at an individual rather than a global level. The complete sequencing of microbial genomes will help us understand what makes some strains of bacteria more virulent than others and will aid in the development of more effective therapeutic interventions.

There are also challenges involved in the management and use of information generated by the Human Genome Project. It will be important to anticipate how this information might be used in ways that are unethical or detrimental to individuals or groups of people. Information about genetics and genetic research is reported almost daily in newspapers and magazines and on the radio, television, and Internet. This often means that a patient may hear of a new discovery before it is published in a scientific journal. Health professionals must be prepared to answer patients' questions and know how and where to refer them for additional information or counseling. Practicing dental clinicians provide the front line as diagnosticians and for referral of patients and families for genetic testing and counseling for many oral health conditions. This requires a basic understanding of the genetics of human disease, knowledge of the types of genetic testing that are available, and sensitivity to the family's concerns.

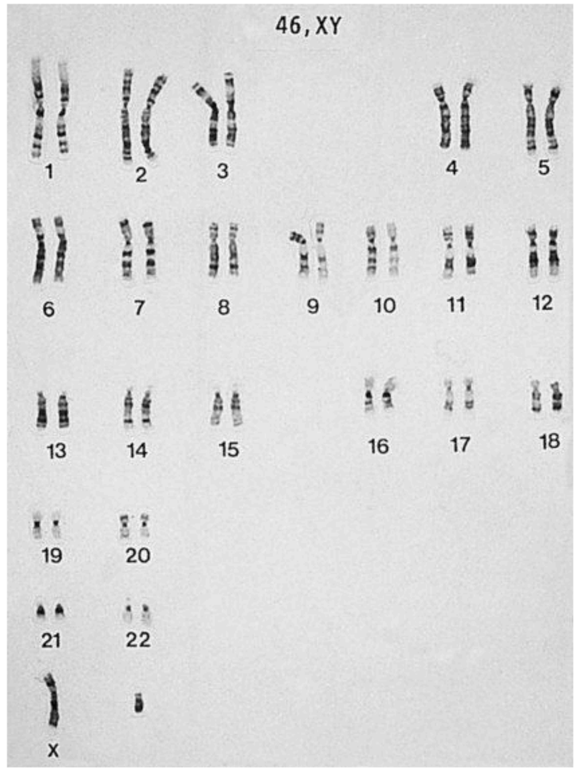
Practicing dentists are confronted daily with conditions that are either primarily genetic or have a significant genetic contribution in their etiology. Common conditions such as congenitally missing teeth now are known in many cases to be caused by specific genetic mutations. Many syndromes involve craniofacial structures and have associated dental anomalies. Frequently, other major malformations are present in addition to the craniofacial anomalies. Advances in the Human Genome Project have led to the discovery of the genetic basis of many of these disorders that have craniofacial and dental anomalies as part of the spectrum of the disease. Understanding the disease at this level permits the practitioner to provide more precise diagnosis of the disease, more appropriate treatment, and more accurate prognosis of the outcomes of care.

Dental practitioners are aware of the environmental and behavioral risk factors that contribute to poor oral health. We routinely counsel our patients and their parents about the risks involved with cigarette smoking, smokeless tobacco, alcohol, poor oral hygiene, sweetened beverages, a diet high in carbohydrates, and traumatic injuries to the head and mouth. We know that the two most common dental diseases—dental caries and periodontal disease—are complex and have both environmental and genetic components. As we continue to gain information about the genetic makeup of individuals, there will be additional genetic susceptibility or resistance factors identified that will influence the severity of oral diseases. Once these factors are identified, there will be tests that can be performed well before the occurrence of disease. This will permit practitioners to educate patients about the importance of their behaviors and to tailor their preventive strategies more specifically for each patient. There will be some tests that dentists can perform in their offices, whereas others will require the use of an outside laboratory. The application of appropriate tests and ultimately the interpretation of the test results and the management of the oral disease will be the responsibility of the dentist. Therefore practicing dentists must understand the basis of the test, how it is performed, and how the results are interpreted. Understanding the basis for many of the genetic tests available today requires an understanding of basic genetic concepts as well as the current technologies that are available for testing.

Basic Genetic Concepts

A person's genome is made up of the DNA in all 46 chromosomes in the nucleus of each cell of the body. Each cell has 23 pairs of chromosomes. One chromosome of each pair is inherited from each parent. Two of the chromosomes are called sex chromosomes (X and Y), whereas the remaining chromosomes (numbered 1 through 22) are called autosomes. Males have one X and one Y chromosome; females have two X chromosomes. In each cell of a female, one of the X chromosomes is randomly inactivated. This is an important determinant of the severity of X-linked genetic disorders, as will be discussed later. The tool used to look at all of the chromosomes in a cell and to determine the sex of a fetus from amniotic fluid is called a karyotype (Figure 16-1). This technique also identifies major chromosomal anomalies such as trisomy (an extra chromosome), translocations of one part of a chromosome to another, or

large chromosomal deletions.



■ FIGURE 16-1 Karyotype of a normal male.

Each chromosome is made up of double-stranded DNA helix composed of a series of four nucleotides and a sugar-phosphate base. Each of the four nucleotides (adenine, thymine, cytosine, and guanine) is paired with a specific complementary nucleotide to form the double helix. Adenine always pairs with thymine, and cytosine always pairs with guanine. The ability of a single strand of DNA to bind to a complementary strand of DNA or RNA forms the basis of many of the diagnostic tests performed today.

Genes are sequences of DNA that are transcribed into messenger RNA and then translated into proteins. Each chromosome contains thousands of genes. The entire human genome is estimated to have between 35,000 and 50,000 genes. The exquisite control of gene expression is essential for the proper growth, development, and functioning of an organism.

Although each cell contains the same DNA and therefore the same genes, only a small percentage of those genes are active or expressed depending on the time of development and the type of cell. Cells in the epidermis need different proteins than cells in the developing tooth or in the kidney, and each cell type has a complex regulatory process to ensure that the right genes are expressed and translated into the necessary proteins at the proper time.

Molecular Basis of Disease

Traditionally, genetic diseases have been thought of in terms of Mendelian inheritance patterns. This means that a mutation present in a gene transmitted to a child from one or both parents results in the child's either having the disease or being a carrier of the disease. As we have learned more about genetics, additional mechanisms of inheritance have been identified that make it more challenging to predict both the occurrence and the severity of disease. It is not uncommon for a genetic disease to be the result of a new mutation. In this case, there would be no history of the disorder on either side of the family. Other types of nonmendelian inheritance patterns include imprinting, DNA triplet repeat expansion, mitochondrial DNA defects, and complex disorders in which multiple genes may be involved and in which sequence changes increase or decrease a person's susceptibility to disease.

Inheritance Patterns

Autosomal Dominant

In autosomal dominant inheritance, the transmission is vertical from parent to child. An affected parent has a 50% chance of passing along the defective gene to either sex child. It may occur in the family initially as a new mutation or may have been present in the family for multiple generations. Dentinogenesis imperfecta is an example of an autosomal dominant disorder. The gene for type I dentinogenesis imperfecta has been identified (dentin sialophosphoprotein) and is located on chromosome 4. Other autosomal dominant disorders include achondroplasia (short-limbed dwarfism), some forms of amelogenesis imperfecta, and Marfan syndrome.

Autosomal Recessive

An autosomal recessive disorder is only manifest when an individual has two copies of the mutant gene. Most frequently, each parent has one copy of the defective gene and is a carrier, and there is a 25% chance that both mutant genes will be passed on to their offspring. It is equally likely that males and females will be affected. Fifty percent of the time the offspring will get one copy of the mutant gene from one parent and will be a carrier, and 25% of the time the offspring will get two normal copies of the gene. Although autosomal recessive disorders are relatively uncommon, the carrier status in certain populations can be significant. For example, 1 in 25 people of northern European descent are carriers of cystic fibrosis.[1]

X-Linked

Mutations in genes located on the X chromosome result in X-linked genetic disorders. Since females have two X chromosomes and one is randomly inactivated in each cell, they are carriers and do not normally manifest the disorder. Males, on the other hand, only have one X chromosome, which is inherited from their mother. A son has a 50% chance of inheriting the defective gene from his mother and manifesting the disease. A daughter also has a 50% chance of inheriting the defective gene from her mother but will then be a carrier. X-linked disorders often appear to skip a generation because an affected male will only pass the affected X chromosome to a daughter and she will serve as a carrier to the next generation. Disorders with X-linked inheritance include factor VIII deficiency (hemophilia), X-linked hypohydrotic ectodermal dysplasia, fragile X syndrome, and X-linked amelogenesis imperfecta. Occasionally, as a result of nonrandom X inactivation, females may have mild symptoms of an X-linked disorder.

Chromosomal Anomalies

In the previous examples, defects in one or both copies of a gene were responsible for the occurrence of a genetic disorder. Some disorders result from defects in chromosomes that result in extra copies of one or more genes, entire deletions of one or more genes, or translocation of one part of a chromosome with another. Generally, chromosomal anomalies result in multiple physical defects as well as mental and developmental delay. Down syndrome is the result of a trisomy (three copies) of all or part of chromosome 21. The duplicated part of the chromosome leads to an extra copy of all the genes on that part of the chromosome. The dosage of gene products in each cell is highly regulated. Extra copies of genes lead to excess gene products that interfere with the necessary balance in the cell. Extra or missing chromosomal material frequently results in miscarriages and/or multiple birth defects.

Multifactorial Inheritance

Most common diseases of adulthood (such as diabetes, hypertension, and manic depression) as well as most congenital malformations (cleft lip/palate and neural tube defects) are the result of multiple genes and gene-environment interactions, rather than a single gene defect. This is also true for the most common dental diseases (periodontal disease and dental caries). Multifactorial traits are thought to result from the interaction between multiple genes with multiple environmental factors. The most convincing evidence for this type of inheritance comes from twin studies. If a trait is multifactorial with a significant genetic component, monozygotic (identical) twins will both have the disease significantly more frequently than dizygotic (fraternal) twins. This has been demonstrated in multiple studies for dental caries among twins raised apart and provides strong evidence that there is a genetic

component to dental caries susceptibility.[2,3] More recently, researchers have completed a genome-wide association study to identify genetic loci associated with the susceptibility or resistance to dental caries.[4]

Nontraditional Inheritance

Other types of inheritance patterns that do not fit the traditional Mendelian patterns and that have been identified fairly recently are *imprinting* and *triplet repeat expansion*. Imprinted genes are turned off by methylation of the gene. This process controls the level of expression of a particular gene in the offspring. Depending on whether the imprinted gene is inherited from the mother or father determines if the child has a particular disease. In some cases, if the imprinted gene is inherited from the father, the child has one disease, but if the same imprinted gene is inherited from the mother, he or she has a different disease.

DNA triplet repeat expansion is a phenomenon where strings of repeated nucleotides increase in number. For example, within a particular gene, there may be 200 copies of the trinucleotide repeat "TAG." Smaller numbers of repeats are often referred to as a premutation, but when the repeats are expanded in an offspring, they may cause the gene to be inactivated (often by methylation). Diseases caused by this type of defect include Huntington chorea and fragile X syndrome.

Epigenetic mechanisms affect the expression of genes and can be caused by environmental chemicals, developmental processes, drugs, or aging. These changes are not the result of DNA sequence alterations but rather are caused by factors such as DNA methylation and histone acetylation. Although the term *epigenetics* was coined in 1942, its relevance to inheritance of disease susceptibility has attracted substantial attention in recent years.

Dentist as Dysmorphologist

The word *dysmorphic* describes faulty development of the shape or form of an organism. Facial features in a child are frequently referred to as dysmorphic when they vary from what is considered normal. Features such as the spacing between the eyes, the position and shape of the ears, and the relative proportions of the maxilla and mandible either are within the range of normal or vary enough to be considered dysmorphic. Many genetic syndromes result in dysmorphic facial features that frequently help to diagnose the syndrome. For example, children with Down syndrome have inner epicanthal folds, up-slanting palpebral fissures, and maxillary hypoplasia. This causes unrelated children with Down syndrome to have a similar appearance to each other.

There are four basic mechanisms that result in structural defects during development. The first is malformation, the second is deformation due to mechanical forces, the third is disruption where there is a breakdown of tissues that were previously normal, and the fourth is dysplasia. Dysplasia is caused by a failure of normal organization of cells into tissues. It is not uncommon for humans to have at least one "minor" malformation. This includes things such as hair whorls, inner epicanthal folds, aberrant positioning of oral frenula, or preauricular pits. Although the occurrence of single anomalies such as these are relatively common and often present as a familial trait, there are a number of studies that have demonstrated that a child who has three minor anomalies has a much greater chance of having a major anomaly such as a defect in brain or heart development.[5-7] This illustrates why it is important for health care professionals to be careful observers of their patients and to be familiar with the facial features that are considered to be normal or aberrant.

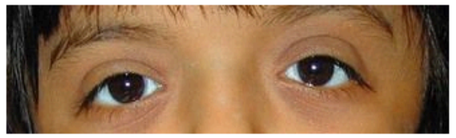
In general, the children seen in a dental practice fit into one of three categories. They may be normally developed in every way; they may have been diagnosed with a developmental anomaly of some type (either physical or mental); or they may have a developmental anomaly that has not been diagnosed. Pediatric dentists and general dentists are in the unique position of seeing their patients regularly, even when the patient does not perceive a dental problem. This is in contrast to the typical physician who may only see patients when they are ill. This frequent interaction between dentists and their patients gives the dentist the opportunity to observe a child's growth and development and to note changes that are not within the range of normal. As health care professionals, it is incumbent on all dentists to recognize disease in their patients and to make the appropriate referral for definitive diagnosis and treatment.

Dentists are trained to observe and examine the mouth, face, and other craniofacial structures. Coincidentally, many inherited diseases in humans involve malformations of the craniofacial region. Accurate diagnosis of developmental anomalies and their related disorders relies on the ability of the clinician to recognize and differentiate between normal and dysmorphic physical characteristics. According to the text *Smith's Recognizable Patterns of Human Malformation*, 12 of the 26 categories of malformations used for diagnostic purposes involve features of the head or neck.[8] Several are limited to oral structures, such as hypodontia, microdontia, micrognathia, and cleft lip/palate. In addition, having an understanding of the full spectrum of malformations associated with certain syndromes is essential for the safe and effective treatment of patients with these disorders.

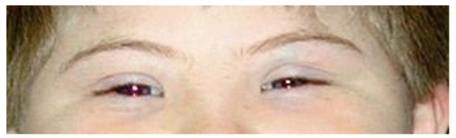
Because dentists concentrate their diagnostic expertise on the face and mouth, they may be more likely to observe anomalies that are suggestive of major developmental malformations. Dentists who can recognize potential genetic disorders can also provide a valuable service to their patients by offering appropriate referral to a medical geneticist or a genetic counselor.

Ocular Anomalies

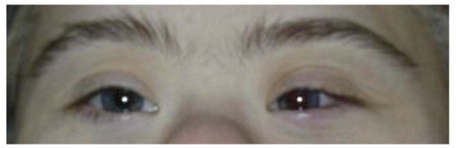
Minor anomalies that affect the eyes and ocular region include widely spaced eyes (hypertelorism) (Figure 16-2), inner epicanthal folds (Figure 16-3), slanting of the palpebral fissures (upward or downward) (Figures 16-4 and 16-5), a single eyebrow (synophrys), blue sclera, and coloboma of the iris (cat-eye) (Figure 16-6).



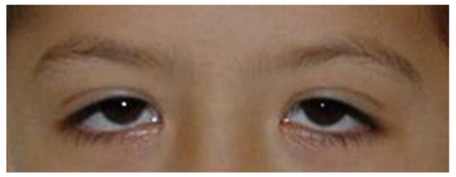
■ **FIGURE 16-2** Hypertelorism.



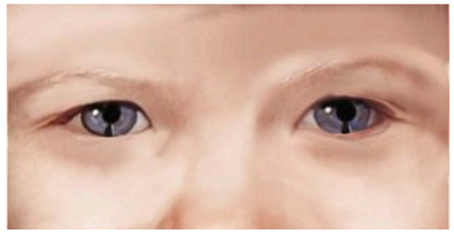
■ **FIGURE 16-3** Inner epicanthal fold.



■ **FIGURE 16-4** Up-slanting palpebral fissures.



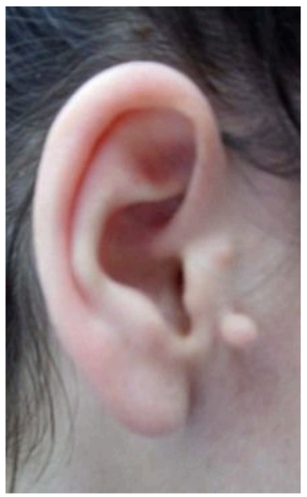
■ **FIGURE 16-5** Down-slanting palpebral fissures.



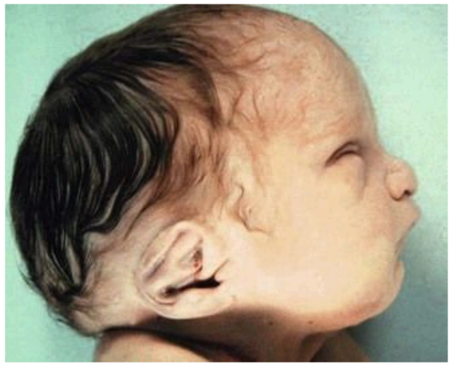
■ **FIGURE 16-6** Coloboma of the iris. (From Kaban LB, Troulis MJ: *Pediatric oral and maxillofacial surgery,* St Louis, 2004, Saunders.)

Auricular Anomalies

There are a number of minor anomalies that affect the outer ear (auricle) and the preauricular region. These include preauricular tags or pits (Figure 16-7), low-set and malformed ears (Figure 16-8), protruding ears, and slanted ears.



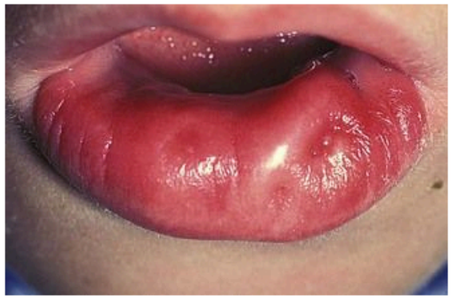
■ **FIGURE 16-7** Ear tag.



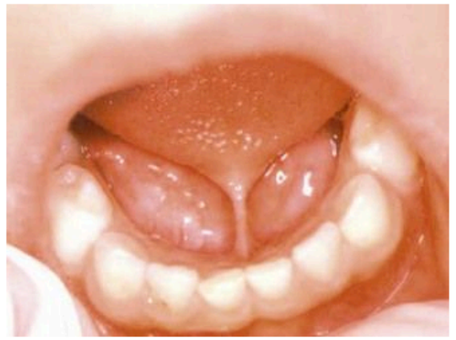
■ **FIGURE 16-8** Low set and malformed ears. (From Gilbert-Barness E, Kapur RP, Oligny LL et al: *Potter's pathology of the fetus, infant and child,* ed 2, St. Louis, Mosby, 2007.)

Anomalies of the Mouth and Oral Region

Cleft lip alone or combined with a cleft palate, although not a minor anomaly, can occur independently from other malformations and is then considered nonsyndromic. Other anomalies in this region include lower lip pits (Figure 16-9), bifid uvula, macroglossia, and prominent or full lips. Attached frenula as is seen with ankyloglossia (Figure 16-10) is also a fairly common anomaly in the oral region.



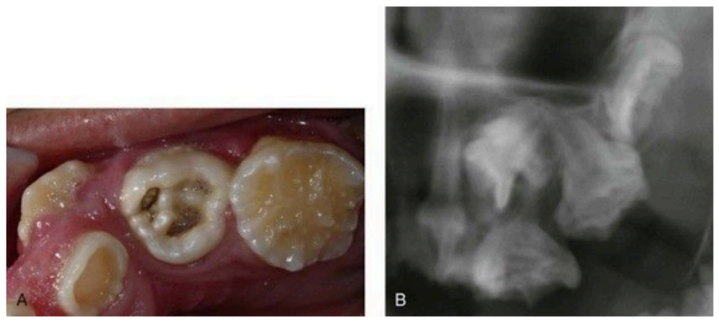
■ **FIGURE 16-9** Lower lip pits.



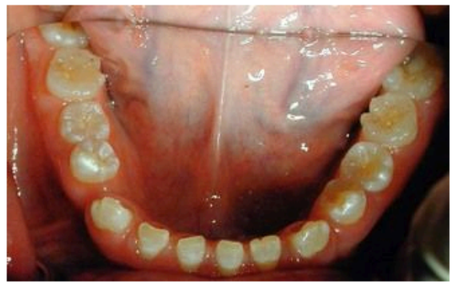
■ **FIGURE 16-10** Ankyloglossia.

Dental Anomalies

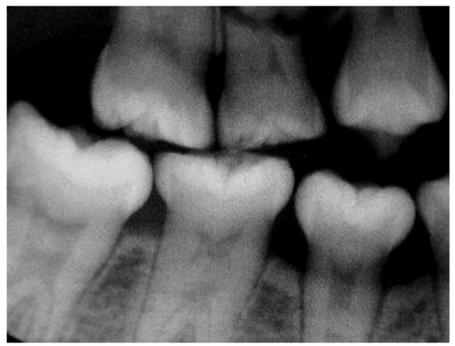
Anomalies of tooth development are relatively common and may occur as an isolated finding or in association with other minor and major anomalies. Hypodontia is the developmental absence of one or more primary or permanent teeth. Although there are a number of syndromes in which hypodontia is a feature, the occurrence of one or more missing teeth (other than third molars) is estimated to be 6%. Anomalies of teeth follow patterns that reflect the time in development when the malformation occurs. For example, disruptions in tooth initiation result in hypodontia or supernumerary teeth, whereas disruptions during morphodifferentiation lead to anomalies of size and shape such as macrodontia (Figure 16-11), microdontia (Figure 16-12), taurodontism (Figure 16-13), and dens invaginatus (Figure 16-14). Disruptions that occur during histodifferentiation, apposition, and mineralization result in dentinogenesis imperfecta (Figure 16-15), amelogenesis imperfecta (Figure 16-16), dentin dysplasia, and enamel hypoplasia (Figure 16-17).



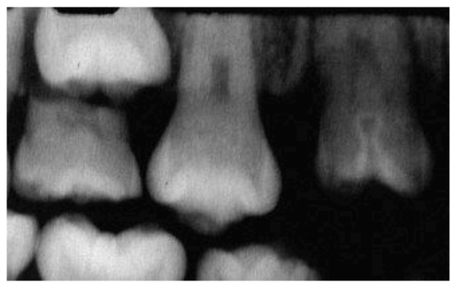
■ **FIGURE 16-11** Clinical (**A**) and radiographic (**B**) images of primary molars with macrodontia.



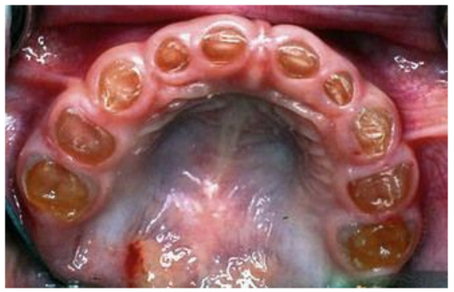
■ **FIGURE 16-12** Permanent teeth with microdontia.



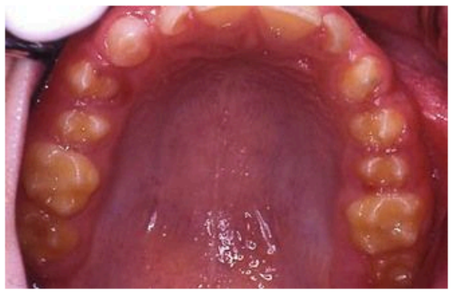
■ **FIGURE 16-13** Radiographic image of permanent molars with taurodontism.



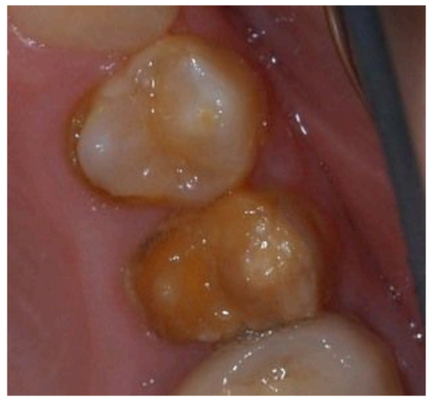
■ **FIGURE 16-14** Radiographic image of permanent canine with dens invaginatus.



■ **FIGURE 16-15** Dentinogenesis imperfecta in the primary dentition.



■ **FIGURE 16-16** Amelogenesis imperfecta in the permanent dentition.



■ **FIGURE 16-17** Enamel hypoplasia of a permanent second premolar.
(Courtesy Dr. John Warren, University of Iowa, Iowa City, Iowa.)

Aside from managing the oral health of patients, a dentist's first responsibility is to recognize disease, whether it is in the mouth or in another part of the body. The second responsibility is to know what to do when anomalies are identified in a patient. We are fortunate to be in an era where there is a wealth of information at our fingertips. With access to a computer and the Internet, both health care practitioners and the lay public can find information about a specific disorder in minutes. There are a number of extremely valuable and reliable resources on the Internet including databases of published research articles, databases for inherited or rare diseases, and websites dedicated to information about specific syndromes (Box 16-1). For those without access to the Internet, there are a variety of valuable and frequently updated textbooks that provide information about syndromes that have craniofacial anomalies.[8,9]

■ **Box 16-1 Sources of Genetic Information**

National Center for Biotechnology Information: www.ncbi.nlm.nih.gov/entrez/query.fcgi
Online Mendelian Inheritance in Man: www.ncbi.nlm.nih.gov/omim
National Human Genome Research Institute: www.genome.gov/
National Coalition for Health Professional Education in Genetics: www.nchpeg.org/
Genetic Alliance: geneticalliance.org/
Gene Expression in Tooth: bite-it.helsinki.fi/
National Organization for Rare Disorders: www.rarediseases.org/
National Foundation for Ectodermal Dysplasias: www.nfed.org/
National Society of Genetic Counselors: www.nsgc.org/
American Society of Human Genetics: www.ashg.org/
National Newborn Screening and Genetics Resource Center: genes-r-us.uthscsa.edu/
March of Dimes: www.marchofdimes.com/
FACES: The National Craniofacial Association: www.faces-cranio.org/
Wide Smiles Cleft Lip and Palate Resource: www.widesmiles.org/
American Cleft Palate-Craniofacial Association: www.acpa-cpf.org/

Why is it important for dentists to pay attention to potential developmental problems with their child patients, and what should dentists do if a developmental anomaly or syndrome is suspected? First, the dentist is responsible for the patient's overall health, not just the health of the mouth or teeth. Patients rely on health care providers to

diagnose problems and inform them of those problems so they can get appropriate and timely treatment. Second, there are many syndromes with features that influence how a dentist provides care for patients. For example, many children with Noonan syndrome have a congenital heart defect that may require the use of prophylactic antibiotics before dental treatment. Patients with Down syndrome frequently have congenital cardiac anomalies and, in addition, are at higher risk for periodontal disease as adults. Both of these characteristics require that a dentist modify the way he or she provides treatment to such patients.

When an anomaly is suspected but not diagnosed, the dentist should know how to gather the appropriate background information from the parent and, if necessary, refer the patient to a medical geneticist for further evaluation. Most teaching hospitals have a department of medical genetics that a child could be referred to for evaluation. In some areas, there are also outreach clinics where medical geneticists and genetic counselors travel to smaller towns to evaluate patients. Availability of genetic counselors in a particular area can be determined from the website of the National Society of Genetic Counselors (www.nsgc.org/FindaGeneticCounselor/tabid/64/Default.aspx). The database can be searched by entering a zip code and the number of miles a patient is able or willing to travel for care. Alternatively, practitioner name, practice type, or location can be used as search queries. As with any referral, it is important to send a letter to the physician or genetic counselor explaining why you are sending the patient for evaluation.

When discussing potential developmental anomalies with parents, it is important to be very sensitive to their concerns and to avoid causing undue alarm. Depending on the circumstances, it may be best to observe the child at multiple appointments (assuming there are treatment needs) and to get to know the family better before broaching the subject. On the other hand, when there are clear or obvious concerns and a timely diagnosis is indicated, an immediate referral should be made. One disorder that a dentist is likely to be the first to diagnose is ectodermal dysplasia. Frequently, parents become concerned when their 2- or 3-year-old child does not have any visible teeth or has conically shaped teeth. This should be recognizable to a dentist who sees children as a developmental anomaly that should be further investigated. At this age, children frequently also have sparse hair, but the combination of hypodontia, sparse hair, and dry skin should cause a dentist to refer this child to determine if he or she has a form of ectodermal dysplasia. Similarly, if a child who is 10 or 12 years old has not lost any primary teeth, a dentist should investigate further to determine the reason the teeth have not exfoliated. In children with cleidocranial dysplasia, multiple supernumerary teeth are present that block the eruption of the permanent teeth; but there is also a genetic defect that keeps teeth from erupting even after the supernumerary teeth are removed.

Because the genetic defects that cause many dominantly inherited syndromes can occur as new mutations, frequently the child is the first person in the family to experience the disorder. It is always important to ask about family history of disease, but absence of disease in the family does not preclude the occurrence of disease in the offspring.

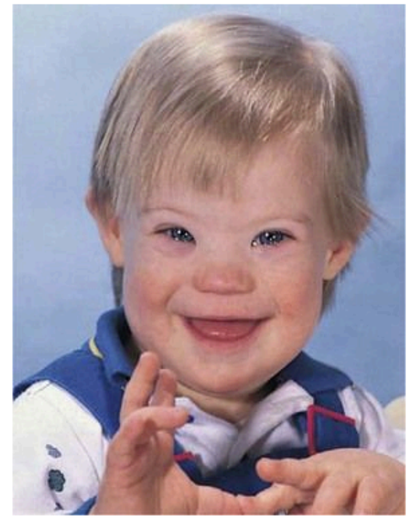
When the child has already been diagnosed with a particular disorder, frequently the disorder is rare enough that a dentist may not have heard of it. In this case, it is important to gather as much information about the characteristics of the disorder before treating the child. Again, one of the most useful resources for this is the Internet. The database known as Online Mendelian Inheritance in Man (OMIM; www.ncbi.nlm.nih.gov/omim) is maintained and updated regularly by Johns Hopkins University. The database can be searched by entering the name of the syndrome or by entering clinical characteristics of the syndrome, such as hypodontia and sparse hair. After searching for a particular term, the database will give a list of disorders that include that term within the text of the description of the disorder. In addition, there are references that are linked to the National Library of Medicine database of published literature, PubMed (see Box 16-1), so that abstracts for articles about the disorder can be easily accessed or downloaded. This is a free database that is available to anyone with an Internet connection. Information about syndromes is also available via the National Organization for Rare Disorders (NORD; www.rarediseases.org/). This site also has a large database of rare diseases. To view full reports of a disease you must be registered. Two reports per day are available at no charge to registered users. There is currently no charge for registration.

Syndromes with Craniofacial Anomalies

It is not possible in a single chapter to discuss every syndrome that includes malformations involving the face or mouth. The following section focuses on a subset of these disorders that are either more commonly seen in the dental office or have such dramatic dental and oral manifestations that all dentists should be aware of them. It is recommended that every dental office has access to information about genetic disorders via both the Internet and one or more textbooks.

Down Syndrome

Inheritance pattern: Chromosomal; sporadic
Gene(s): Trisomy 21
General manifestations: Mental deficiency; hypotonia; cardiac anomaly in about 40% of cases; dry skin; increased risk for leukemia (ALL and AML)
Craniofacial/dental manifestations: Brachycephaly; inner epicanthal folds; up-slanting palpebral fissures; small ears; microdontia; decreased risk for dental caries; increased risk for periodontal disease; increased risk for atlantoaxial instability[8]
Dental treatment considerations: When treating children with Down syndrome (Figure 16-18), the primary concerns are to determine the need for subacute bacterial endocarditis prophylaxis and the child's ability to cooperate. If a child has had surgery to repair a congenital heart defect, he or she may or may not need subacute bacterial endocarditis prophylaxis, depending on when the surgery was performed and on the presence of any residual defect. This should be confirmed with the parent or the child's cardiologist. The behavior of children with Down syndrome varies from one child to another just as it does for normally developed children. It is not fair to assume in advance that a child will be uncooperative for dental treatment. On the other hand, some children and young adults with Down syndrome are extremely stubborn and very difficult to examine in the traditional dental setting. When behavior is an issue, it may be necessary to use oral sedation, general anesthesia, and/or referral to a specialist in order to provide quality care for the patient. It is important to note that patients with Down syndrome are much more susceptible to periodontal disease. The dentist should make this clear to the parent and should stress early development of good oral hygiene habits including thorough, supervised daily toothbrushing with a fluoridated toothpaste, flossing, and, when necessary, the use of an antibacterial mouth rinse such as 0.12% chlorhexidine.

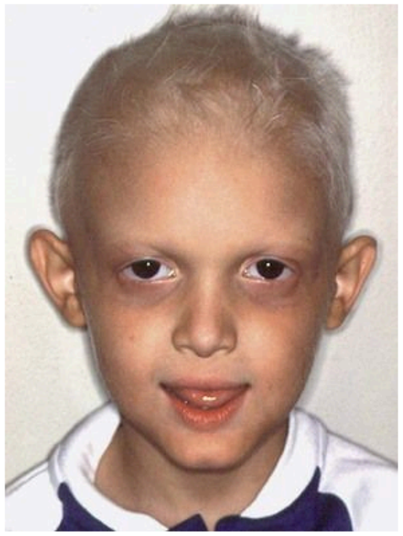


■ **FIGURE 16-18** Typical facies of a child with Down syndrome including flat nasal bridge, epicanthal folds, and up-slanting palpebral fissures.
(From Zitelli BJ, Davis HW: *Atlas of pediatric physical diagnosis*, ed 5, Philadelphia, 2007, Mosby.)

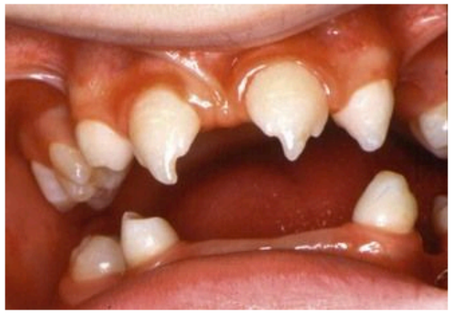
Ectodermal Dysplasia/Hypodontia

Inheritance pattern: X-linked recessive, autosomal dominant, autosomal recessive
Gene(s): Ectodermal dysplasia 1 *(ED1)*[10]; ectodysplasin 1 *(EDAR)*[11]; muscle segment homeobox homolog 1 *(MSX1)*[12]; paired box gene 9 *(PAX9)*[13]

General manifestations: Sparse hair; dry skin; absence of sweat glands; normal mental status[8]
Craniofacial/dental manifestations: Full lips; small nose; hypodontia; conical or malformed teeth; deficient alveolar ridge
Dental treatment considerations: There are more than 150 forms of the ectodermal dysplasia syndromes that affect one or more of the tissues derived from the ectoderm (Figures 16-19 and 16-20). Although the most well-known condition is the X-linked anhidrotic form, there are also autosomal dominant and autosomal recessive forms with symptoms that range from mild with hypodontia only to severe with many structures affected along with a cleft lip and palate (ectrodactyly–ectodermal dysplasia–clefting syndrome). Children with ectodermal dysplasia frequently lack most primary and permanent teeth. This leads to underdevelopment of the alveolar ridges and makes fabrication of dentures much more challenging.



■ **FIGURE 16-19** A child with ectodermal dysplasia showing sparse hair.
(From Proffit WR, Fields HW, Sarver DM: *Contemporary orthodontics*, 5 ed, St Louis, 2013, Mosby.)



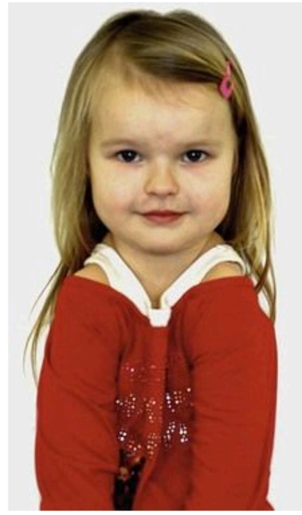
■ **FIGURE 16-20** Dentition of a child with ectodermal dysplasia demonstrating missing lower incisors and malformed central incisors.

When ectodermal dysplasia is inherited as an X-linked or autosomal dominant disorder, parents are usually familiar with the disorder because other family members are affected. However, the disorder may also be caused by a new mutation or inherited as an autosomal recessive trait. When this happens, the family may be completely unaware of the manifestations of this disorder. It is not uncommon for the dentist to be the first person to recognize ectodermal dysplasia in a child. Parents become concerned when their child has few or no erupted teeth at age 2 to 3 years and asks a dentist to evaluate the child. At this age, it is usually possible to assess the developing teeth using maxillary and mandibular occlusal radiographs. These will establish whether the dental development is delayed, if the primary teeth are missing, or if there is some other process that is interfering with tooth eruption. If primary teeth are not present, the child should be referred to a medical geneticist and/or genetic counselor for a thorough evaluation.

Dentists can provide a great service to children with ectodermal dysplasia by fabricating dentures at a young age and by educating the family about future treatment options. Dentures can be fabricated for young children as soon as they are cooperative enough to tolerate impressions. As they grow and mature, other options become available to them including implants and implant-retained dentures. Frequently, bone grafts must be done before placing implants because of the reduced thickness and height of the alveolar ridge. Guidelines for the treatment of these patients at various ages are available from the National Foundation for the Ectodermal Dysplasias (NFED). The publication, entitled *Parameters of Oral Health Care for Individuals Affected by Ectodermal Dysplasia Syndromes,* is available from NFED (http://shop.nfed.org/category/literature/) for $2.00. This organization provides information and support to families who have children with ectodermal dysplasia. Grants are available from NFED for families to help defray the cost of dental treatment and for researchers to better understand the many forms of ectodermal dysplasia.

Cleidocranial Dysplasia

Inheritance pattern: Autosomal dominant or new mutation
Gene(s): Runt-related transcription factor 2 *(RUNX2)*[14]
General manifestations: Moderate short stature; normal intelligence; partial to complete absence of clavicles
Craniofacial/dental manifestations: Frontal bossing; brachycephaly; late closure of fontanels; hypertelorism; delayed eruption of permanent teeth; supernumerary teeth; impacted teeth
Dental treatment considerations: The dental manifestations of this disorder can be extremely challenging and should be approached by a multidisciplinary team including a pediatric dentist, oral surgeon, orthodontist, and prosthodontist (Figure 16-21). The pediatric dentist often serves as the case manager who brings the team together and facilitates communication among the other specialists and the family. Children with cleidocranial dysplasia may have up to 60 supernumerary teeth. Surgical removal of these extra teeth must be done with the appropriate timing and frequently involves multiple surgeries during childhood and adolescence. Once the supernumerary teeth are removed, orthodontic forces are usually required to bring the permanent teeth into position. The timing of this is also crucial, because the appropriate anchorage must be established in advance, and often the first permanent molars are impacted.



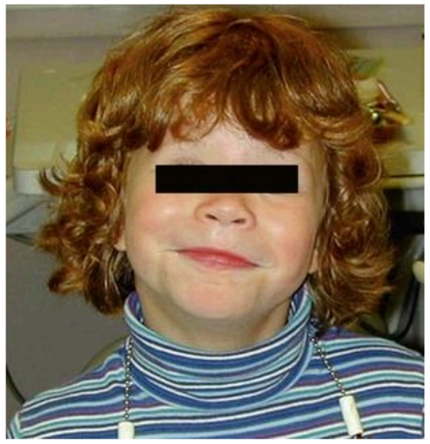
■ **FIGURE 16-21** A child with cleidocranial dysplasia. (From Cobourne MT, DiBiase AT: *Handbook of orthodontics,* Edinburgh, 2010, Mosby.)

It is possible that the delayed eruption of permanent teeth (and delayed exfoliation of primary teeth) will be the first sign that something is abnormal in the child's development. Because this is a relatively rare disorder, and because the general characteristics are not life threatening, it

may go undetected by the child's physician. Again, this is an opportunity for the dentist to provide a service to their patients by recognizing the potential for a genetic condition and referring the child to the appropriate medical facility for definitive diagnosis. Evaluation of a child with retained primary teeth should include a panoramic radiograph and possibly a cone beam computed tomographic scan for enhanced localization and position of teeth.[15] Presence of multiple supernumerary teeth along with one or more of the physical characteristics for this disorder should lead a dentist to refer the family to a medical geneticist for evaluation.

Williams Syndrome

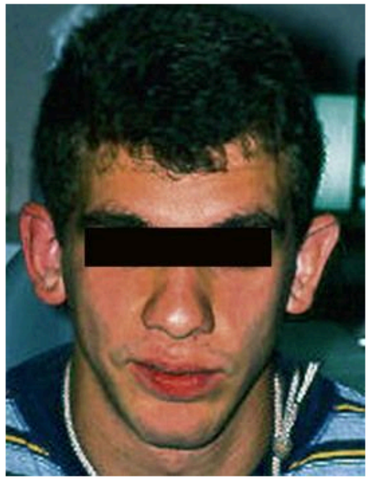
Inheritance pattern: Autosomal dominant or new mutation
Gene(s): 7q11.23 region; elastin *(ELN)*; LIM domain kinase 1 *(LIMK1)*; replication factor C *(RFC2)*[16]
General manifestations: Cardiovascular anomalies; outgoing personality; mental deficiency; hoarse voice
Craniofacial/dental manifestations: Blue eyes with stellate pattern in the iris; hypodontia; enamel hypoplasia; prominent lips; wide mouth
Dental treatment considerations: Children and adults with Williams syndrome can provide both fun and a challenge to your practice (Figure 16-22). Their charming, friendly personality endears them to everyone in the office. However, their hypersensitivity to sound and easy distractibility can make it necessary to spend extra time and patience during dental treatment. Because of the frequent cardiovascular anomalies associated with this disorder, it is essential to determine if there is a need for subacute bacterial endocarditis prophylaxis before dental treatment. If the parent is unsure about this, the dentist should contact the child's cardiologist and document the physician's advice in the patient's record.



■ **FIGURE 16-22** Facies of a child with Williams syndrome.

Fragile X Syndrome

Inheritance pattern: X-linked
Gene(s): Fragile X mental retardation-1 *(FMR1)*[17,18]
General manifestations: Intellectual disability; autism in 60%; macroorchidism[8]
Craniofacial/dental manifestations: Macrocephaly; prognathism; large ears
Dental treatment considerations: Fragile X syndrome is documented as the cause of intellectual disability in almost 6% of males with mental handicapping conditions (Figure 16-23). In the dental clinic, treatment issues primarily center around the child's behavior and ability to tolerate dental procedures. This is complicated further in children who also have autism. As is true for many persons with special needs, their oral health is the responsibility of a parent or other care provider. For this reason, it is important for the dentist to provide the parent with the information and tools required to assess and maintain good oral hygiene and healthy dietary practices for these children.



■ **FIGURE 16-23** A young man with fragile X syndrome.

Dentinogenesis Imperfecta

Inheritance pattern: Autosomal dominant or sporadic
Gene(s): Dentin sialophosphoprotein *(DSPP)*[19]
General manifestations: Normal intelligence; good general health unless in combination with osteogenesis imperfecta
Craniofacial/dental manifestations: Both primary and permanent teeth are affected; teeth are blue-gray or brown; susceptible to extreme wear; pulpal obliteration and dental abscesses
Dental treatment considerations: The severity of this disorder varies considerably from one child to another both within and between families (see Figure 16-15). In addition, the appearance of the primary dentition does not reliably predict the appearance of the permanent dentition. In the primary dentition, stainless steel crowns are frequently used to prevent excessive wear of the molars. This should be initiated once wear is apparent on the molars. For some children this may occur as early as 2 years of age, whereas for others it may occur later. Abscessed primary teeth require pulp therapy but may need to be extracted if significant pulpal obliteration has occurred. When aesthetics becomes a concern for the child or family, this can be addressed in the primary dentition using aesthetic anterior crowns or partial overdentures. In the permanent dentition, tray bleaching has been used to lighten the shade of the teeth, and then composite or porcelain veneers may be used on the anterior teeth. As adults, most individuals require full-coverage crowns and frequently root canal therapy. Every effort should be made to maintain the teeth as long as possible to maximize the options the individual has as an adult. Consulting with other dental specialists to assist in planning for future treatment is recommended. If parents report a history of fractures, the child should be referred for a medical evaluation to rule out osteogenesis imperfecta.

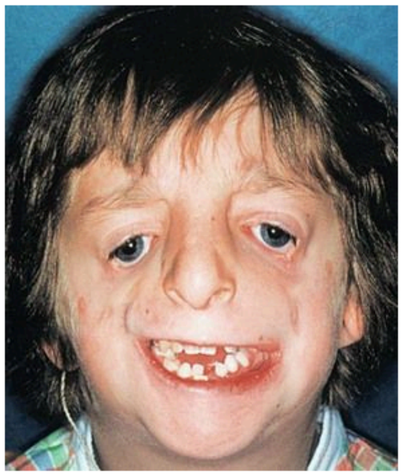
Amelogenesis Imperfecta

Inheritance pattern: Autosomal dominant, autosomal recessive, X-linked, sporadic
Gene(s): Amelogenin *(AMG)*[20]; enamelin *(ENAM)*[21]; family with sequence similarity, member H *(FAM83H)*[22]; matrix metalloproteinase 20 *(MMP-20)*[23]; kallikrein 4 *(KLK-4)*[24]
General manifestations: Normal intelligence; good general health
Craniofacial/dental manifestations: Enamel defects that affect both dentitions; appearance is yellow-brown to orange depending on subtype; teeth may be sensitive, susceptible to wear, and may also have taurodontism in molars
Dental treatment considerations: There are 3 major categories of amelogenesis imperfecta and 14 subtypes. More in-depth discussion of the subtypes can be found in Chapter 3 of this textbook. Dental treatment considerations require that the clinician understand the characteristics of the different subtypes before developing a treatment plan. In general, treatment concerns fit into a few general categories. With most subtypes, the teeth are susceptible to wear and require full crown coverage to minimize this. In the primary dentition, this is usually accomplished by placing stainless steel crowns on all the primary molars. A combination of veneers and full-coverage cast crowns may be used in the permanent dentition. Frequently, transitional restorations must be made during the adolescent years until the permanent teeth are fully erupted. Other

concerns with this group of disorders include tooth sensitivity, aesthetics, susceptibility to dental caries, and malocclusion. It is not unusual for there to be delayed or partial eruption of permanent premolars and molars that require gingival surgery to expose the crown and orthodontic forces to move them into place before restoration. Because of the many complicated issues involved in treating patients with amelogenesis imperfecta, it is recommended that such patients be treated by a team of dental specialists who have had experience with this disorder. When that is not an option because of geographic or other constraints, every effort should be made to consult colleagues who have had experience with this disorder before treatment (see Figure 16-16).

Treacher Collins Syndrome

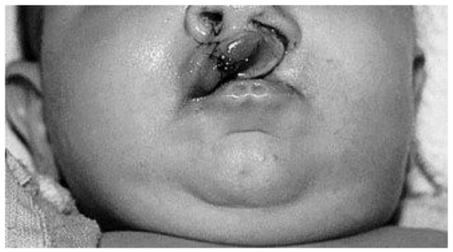
Inheritance pattern: Autosomal dominant or sporadic
Gene(s): Treacher Collins–Franceschetti syndrome 1 *(TCOF1)*[25]
General manifestations: Normal intelligence; conductive deafness; occasional congenital heart defect
Craniofacial/dental manifestations: Down-slanting palpebral fissures; malar hypoplasia; lower lid coloboma; mandibular hypoplasia; malformation of external ear; cleft palate
Dental treatment considerations: The severe micrognathia in some patients with Treacher Collins syndrome contributes to dental crowding and may make intubation difficult if treatment under general anesthesia is required (Figure 16-24). Frequently, orthognathic surgery is required during childhood or adolescence. Dental practitioners should consult with the child's physician to confirm the absence of other medical conditions such as congenital heart defects that might dictate modifications in how dental treatment is delivered.



■ **FIGURE 16-24** Facies of a child with Treacher Collins syndrome. (From Nanci A: *Ten Cate's oral histology: development, structure, and function*, ed 8, St Louis, 2013, Mosby.)

Van Der Woude Syndrome

Inheritance pattern: Autosomal dominant or sporadic
Gene(s): Interferon regulatory factor 6 *(IRF6)*[26]
General manifestations: Normal intelligence; good general health
Craniofacial/dental manifestations: Lower lip pits; cleft lip/palate; cleft uvula; hypodontia
Dental treatment considerations: Cleft lip and/or palate may occur as a solitary finding or as part of a syndrome (Figure 16-25). Children with Van der Woude syndrome may have lower lip pits alone or in combination with cleft lip and/or cleft palate. Because the symptoms are limited and because affected individuals have normal intelligence, this disorder could be confused with nonsyndromic cleft lip/palate. It is important that children with cleft lip/palate or with lip pits only be seen and evaluated by a craniofacial anomalies team to determine the cause and heritability of their disorder. In addition, this type of team approach is important for providing coordinated, timely treatment of children with cleft lip/palate. Most hospitals have cleft lip/palate or craniofacial teams that include specialists from the following disciplines: plastic, craniofacial and/or oral surgery, pediatric dentistry, orthodontics, speech pathology, prosthodontics, social work, and medical genetics.



■ **FIGURE 16-25** Cleft lip/palate in a child with Van der Woude syndrome.

Osteogenesis Imperfecta

Inheritance pattern: Autosomal dominant or sporadic
Gene(s): Type I collagen *(COL1A1, COL1A2)*[27]; cartilage associated protein *(CRTAP)*[28]; prolyl 3-hydroxylase 1 *(LEPRE1)*[28]
General manifestations: Moderate to severe bone fragility; short stature; normal intelligence; hearing impairment in adulthood; hyperextensible joints; deformity of limbs
Craniofacial/dental manifestations: Triangular facies; blue sclera; occasional dentinogenesis imperfecta; delayed eruption of teeth
Dental treatment considerations: Osteogenesis imperfecta is a heterogeneous disorder resulting from both quantitative and qualitative defects in type I collagen and from mutations in two recently identified genes *(CRTAP, LEPRE1)*.[28] There are eight distinct subtypes of osteogenesis imperfecta with symptoms that range from mild to severely deforming to lethal. Osteogenesis imperfecta type I is the mildest form and may go undiagnosed until the child's first fracture. In some cases, parents of children with an undiagnosed mild form of osteogenesis imperfecta have been accused of child abuse when an unreported previous fracture is detected radiographically. It is important for a physician to rule out osteogenesis imperfecta when questions of previous fractures are being evaluated. Osteogenesis imperfecta type II is lethal at birth or shortly thereafter, and dental professionals are not likely to have exposure to children with this form of the disease. The most severe, deforming variety of osteogenesis imperfecta is type III. These children have extreme bone fragility and by childhood may have had as many as 30 fractures. They are frequently not ambulatory and have a history of surgeries that includes placement of rods in their legs and spine. Osteogenesis imperfecta type IV is intermediate in severity between type III and type I. These children have moderate short stature, bone fragility, and significant bone deformity. Sclera is normal, and often dentinogenesis is present in children with osteogenesis imperfecta type IV. Type V is mild to moderate in severity, type VI is moderate, and types VII and VIII are moderate to severe or lethal.[28] Dental treatment for patients with osteogenesis imperfecta should be done with great care and with guidance from the parent to determine what the child can tolerate. Active or passive immobilization of patients with osteogenesis imperfecta is not recommended for obvious reasons. If behavior at a young age makes treatment in the traditional dental setting unfeasible, other options such as sedation or general anesthesia should be considered. When a child with dentinogenesis imperfecta presents in a dental office, especially when there is no history of this disorder in the family, the dentist should raise the possibility that the child also has osteogenesis imperfecta. A referral to a medical geneticist for evaluation is appropriate if there is any doubt about the diagnosis.

Hypophosphatasia

Inheritance pattern: Autosomal dominant, autosomal recessive, or sporadic
Gene(s): "Tissue nonspecific" isoenzyme of alkaline phosphatase *(TNSALP)*[29]
General manifestations: Normal or short stature; bone fragility; bowed lower extremities
Craniofacial/dental manifestations: Premature loss of teeth due to lack of cementum; craniosynostosis
Dental treatment considerations: There are four forms of hypophosphatasia that range from mild to lethal. The milder form that presents in childhood

after 6 months of age results in premature loss of primary teeth and craniosynostosis. All types demonstrate decreased levels of serum alkaline phosphatase. Although this is a relatively rare disorder, dentists should be aware of its existence so that an appropriate referral can be made. Frequently, the first sign of this disorder is the premature loss of a mandibular primary incisor without a history of trauma. The exfoliated tooth typically has no root resorption, and histologic analysis will show a lack of cementum. In the mild form of this disorder, the dental manifestations may be the only symptoms.

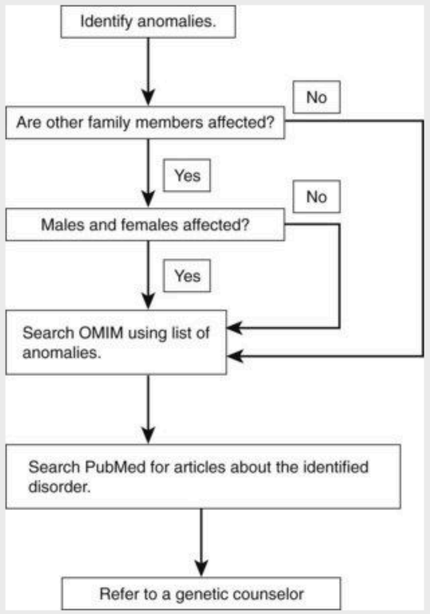
Genetic Testing

The majority of genetic tests available today are used to diagnose specific inherited disorders such as cystic fibrosis, Huntington disease, or fragile X syndrome. These tests are performed and interpreted by medical geneticists or genetic counselors for the most part. Genetic tests for inherited disorders involve screening for specific mutations or chromosomal disruptions. A second category of genetic tests screens for genetic risk factors for various disorders that have a genetic component. This includes disorders such as familial breast cancer and Alzheimer disease. Testing positive for one of these risk factors does not guarantee that one will get the disease, but it does indicate that an individual is at increased risk of developing the disease. This information allows one to make changes in their life to decrease other risk factors for that disease. Identification of genetic risk factors for dental caries and for periodontal disease is the goal of a number of dental researchers. It is conceivable that in the near future in-office genetic tests will be available to determine the caries risk or periodontal disease risk of an individual patient. Using the results of these tests, the dentist will be able to develop a targeted prevention plan to minimize the severity of disease for that individual.

Decision Tree to Assess Inherited Disorders

Most dentists recognize the importance of investigating suspected inherited disorders in their patients. However, it may not be something that a dentist is faced with very often, and it is difficult for many private practitioners to know where to start and how to get the necessary information. Access to the Internet has made this task both easier and more complicated at the same time. The purpose of this section is to demonstrate how a dentist with access to the Internet can get information about a genetic disorder and then find the appropriate referral source for the patient. This process will vary somewhat depending on the nature of the disorder, the location of the dental practice, and the dental practitioner's level of experience with the Internet. It is meant to be one example of how a dentist can assist a family in getting the necessary information or treatment needed.

Case 1: David and Matthew are 12-year-old twin boys in good general health. Their mother has brought them to the dentist because she is concerned about the appearance of their teeth and wants to know what options are available to treat them. The clinical and radiographic evaluation of the face and mouth of both boys reveals complete permanent dentition with no dental caries, generalized microdontia, taurodontism of permanent first and second molars, and dens invaginatus of all four permanent canines. The mother is aware that the teeth are unusual and reports that other family members have similar dental findings. One method for investigating this disorder is described below and shown graphically in a decision tree.



1. Do other members of the family have this? *Yes*

   Are both males and females affected? *No; only males are affected.*

2. Has this disorder been described in the literature?

   To determine this, search the Online Mendelian Inheritance in Man (OMIM) database by entering the following URL and the search terms that describe the disorder: www.ncbi.nlm.nih.gov/omim

   Search terms: Microdontia, taurodontism, dens invaginatus.

   Results: One entry with a paper written by Casamassimo and colleagues in 1978. To look for additional references, search PubMed using the author name (Casamassimo) and one or more of the previous search terms.

   Results: Two references are found, the previously mentioned article as well as a second article by Ettinger, Casamassimo, and Nowak that discusses management of a similar case.

3. Should the patient be referred to medical genetics for evaluation?
   - If yes, find a genetic counselor in your area by entering the URL: www.nsgc.org/
   - If no, discuss findings of papers with mother and make plans for necessary treatment.

Ethical, Legal, and Social Implications of the Human Genome Project

In the past, patients have not been denied dental insurance because of preexisting dental disease, and a thorough dental examination is not usually required for a patient to qualify for dental benefits. The result is that dentists may not be aware of the potential for discrimination to which some patients are susceptible because of their health history. Genetic testing that identifies a person's risk for disease before they have any manifestations of the disease introduces a new level of information about an individual's health and insurability that has not been available in the past. Information about risk for disease may interfere with an individual's ability to get a job or to obtain health, life, or disability insurance. In many cases, the ethical, legal, and social implications of the information learned from the Human Genome Project are still being evaluated.

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