REVIEW ARTICLE

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Genetic studies of craniofacial anomalies: clinical implications and applications

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Dates:
Accepted 21 February 2009

To cite this article:
Hart TC, Hart PS:
Genetic studies of craniofacial anomalies: clinical implications and applications
Orthod Craniofac Res 2009;**12**:212–220

Structured Abstract

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The objective of the study was to overview the role of genetic research in fostering translational studies of craniofacial diseases of dental interest. Background information is presented to illustrate influences affecting genetic research studies of Mendelian diseases. Genetic studies of amelogenesis imperfecta, dentinogenesis imperfecta, hereditary gingival fibromatosis and Papillon Lefèvre syndrome are reviewed. Findings are presented to illustrate how translational applications of clinical and basic research may improve clinical care. Clinical and basic science research has identified specific genes and mutations etiologically responsible for amelogenesis imperfecta, dentinogenesis imperfecta, hereditary gingival fibromatosis and Papillon Lefèvre syndrome. These findings are enabling researchers to understand how specific genetic alterations perturb normal growth and development of dental tissues. Identification of the genetic basis of these conditions is enabling clinicians and researchers to more fully understand the etiology and clinical consequences of these diseases of dental importance. Findings from genetic studies of dental diseases provide a basis for diagnostic genetic testing and development of therapeutic intervention strategies directed at the underlying disease etiology. These studies are advancing our understanding of the development of dental tissues in health and disease. The dental community must consider how to incorporate these developments into effective disease prevention paradigms to facilitate the diagnosis and treatment of individuals with genetic diseases.

Key words: dental; diagnosis; genetic diseases; mutation; treatment

Introduction

Of the more than 7000 inherited human disorders, 30–40% display some oral, dental or craniofacial manifestation (1). Certain conditions, such as amelogenesis imperfecta, may affect only mineralized tooth tissues, while others such as hereditary gingival fibromatosis may affect only the gingiva (2, 3). Many other genetic diseases, such as Papillon-Lefèvre syndrome and tricho-dento-osseous syndrome (OMIM190320), affect both oral and extraoral tissues (1). While oral and dental manifestations for some of these diseases are well characterized, they have not been systematically characterized for many genetic diseases. Unique dental and oral findings

are often identified when time is taken to carefully assess the oral cavity (1, 4, 5). Many of these genetic conditions are transmitted within families as Mendelian traits, suggesting that the cause of these conditions may be attributed to genetic alteration of a gene of major effect. With current research approaches it is possible identify genes responsible for these diseases.

Identifying disease genes has been greatly facilitated by advances in genetic research methodologies. As a result, the field of genetics has been transformed into a clinically applied discipline with broad implications for oral medicine (6). While many individual technological advances and discoveries have contributed to the ultimate success of applied genetics research, the successful completion of the human genome project revolutionized genetics research. Collective efforts of an international array of researchers affiliated with academia, private industry and governments integrated efforts in many disciplines to successfully complete the HGP goals (6, 7).

Application of genomic information and technologies has fundamentally altered the way we study human diseases. By applying an ever increasing array of research tools, researchers are able to characterize gene function in health and disease. A vibrant 'Bench to Bedside' clinical research paradigm has emerged, designed to speed translation of promising laboratory discoveries to improve diagnosis and treatment of diseases. Identifying these etiologic genetic alterations provides a first step to enable cellular and molecular studies to characterize how genes function and to understand how alterations of normal gene functions cause disease. The goal of understanding the genetic basis of disease is to facilitate the diagnosis and treatment of disease conditions (Fig. 1). Development of treatments directed at correcting specific biologic defects will permit clinicians to move from a 'one size fits all' treatment approach to a personalized treatment paradigm.

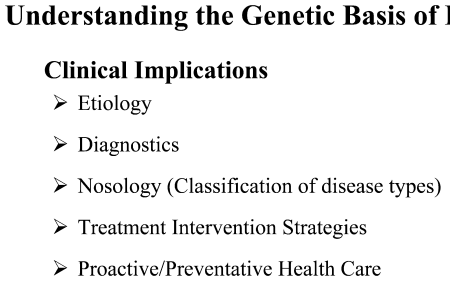


Fig. 1. Clinical implications of understanding the genetic basis of disease.

A first step in identifying the genetic basis of disease has traditionally employed gene mapping strategies. Studying affected and unaffected members of families segregating a genetic disease, researchers employ genetic linkage and genetic association strategies to determine the chromosomal location of disease causing gene(s). Gene mapping studies are often the first step to identifying disease causing genes, permitting their role in normal and abnormal development to be understood. These approaches have identified thousands of disease causing gene mutations, including many that affect dental, oral and craniofacial structures (1), several of which are illustrated below.

Amelogenesis imperfecta

The amelogenesis imperfecta (AI) are a genetically and phenotypically heterogeneous group of disorders that affect the quality or quantity of enamel (2, 8). AI phenotypes are classified as hypoplastic, hypomaturation and hypocalcified. A total of 14 types have been recognized historically based upon phenotype and mode of inheritance. Mutations in five genes have been associated with non-syndromic AI: amelogenin (*AMELX),* enamelin *(ENAM),* family with sequence similarity, member H (*FAM83H),* kallikrein 4 (*KLK4)*, and matrix metalloproteinase 20 (*MMP20)*, improving AI nosology and increasing our understanding of enamel development in health and disease (Fig. 2) (2, 8–10). Mutations of *AMELX*, which encodes the predominant enamel protein amelogenin, are associated with X-linked forms of AI. Mutations of the major enamel proteases, *KLK4* and *MMP20*, are associated with autosomal recessive hypomaturation AI (8). Characterizations of disease associated clinical phenotypes are critical to genetic studies, facilitating a better understanding of genotype-phenotype correlations. For example allelic *ENAM* mutations have been identified in both autosomal dominant and recessive hypoplastic AI (2, 8, 10), and a gene dosage effect has been demonstrated for certain *ENAM* mutations (11). Mutations of the *FAM83H* gene are responsible for the most common form of AI in North America, autosomal dominant hypocalcified AI, (Fig. 2) (12). Despite these

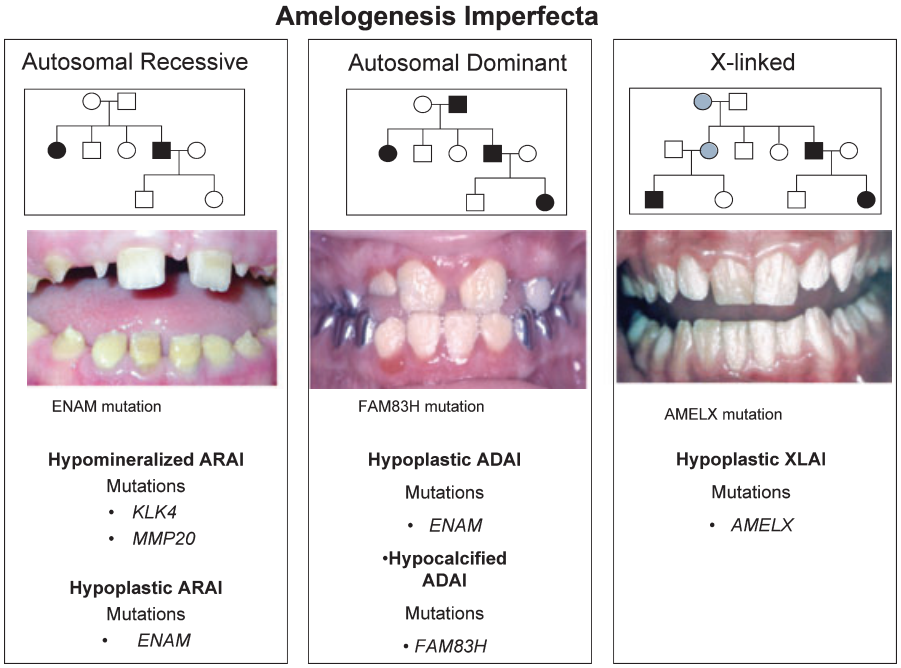


Fig. 2. Amelogenesis imperfecta summary. Genes for which mutations have been identified for each of the Mendelian modes of transmission are illustrated. Clinical photographs illustrating representative examples for each form of Mendelian transmission for AI are shown. The genetic mutation responsible for each case is indicated directly below each photograph. ARAI, autosomal recessive AI; ADAI, autosomal dominant AI; XLAI, X-linked AI).

advances, it is clear that not all AI causing genes have been identified.

Dentinogenesis imperfecta

Dentin defects are broadly classified into the dentinogenesis imperfectas (DIs, types I–III) and dentin dysplasias (DDs, types -I and -II) (13). In DI, the underlying dentin is defective and soft. Although the overlying enamel is structurally normal, it fractures easily, exposing the underling dentin. DI can be an isolated finding due to mutations in the dentin sialophosphoprotein (*DSPP)* gene or as part of a syndrome. Syndromic DI can be a feature of osteogenesis imperfecta, a disorder of brittle bones, that results from mutations in the genes encoding the type-1 collagens: collagen 1A1 (*COL1A1*) and collagen 1A2 (*COL1A2)* (2, 13). In Dentin Dysplasia (DD), the permanent dentition often appears clinically normal, but radiographically the pulp chambers may be obliterated by abnormal dentin. In DD type I, all teeth are normal in shape, form and color, but have short roots, contributing to premature exfoliation. Periapical radiolucencies are frequently noted. Molecular genetic studies have not been performed for DD type I. In DD type II, the deciduous teeth are often clinically indistinguishable from DI. Radiographically, pulp cavities show thistle-tube deformity and commonly have pulp stones. Mutations in *DSPP* have been found to cause DD type II. Until recently it was not possible to sequence the entire coding region of *DSPP* due to a highly repetitive region of the gene. Now that this region can be sequenced, it appears that the majority of *DSPP* mutations occur in this repetitive region (Table 1) (14). The ability to completely sequence the *DSPP* gene has important implications for genetic testing for DI conditions. As the entire *DSPP* gene can now be sequenced, when *DSSP* coding region mutations are not found, the *COL1A1* and *COL1A2* genes can be evaluated for disease causing mutations. We have identified cases of apparently isolated (non-syndromic) DI, in which we have excluded *DSPP* mutations, and subsequently identified *COL1A1* or *COL1A2* mutations. These may reflect very mild cases of OI/DI, where DI is the only clinically apparent phenotypic finding. The ability to determine the genetic basis of DI may have important clinical implications for some families. In such cases, it may be important for families to be aware of individuals who have DI due to collagen type-1 mutations, and for which the clinical expression of disease may vary with some cases presenting only DI, while other cases may show more significant clinical findings affecting bone and vasculature tissues. The ability to determine the etiology of DI in an individual can impact their access to dental care. Definitive genetic testing may be important for individuals to obtain state and/or third party insurance coverage to help with dental care.

Table 1. **Dentin sialophosphoprotein (DSPP) mutations reported for non-syndromic dentinogenesis imperfecta and dentin dysplasia**

Location	cDNA*	Protein†	Diagnosis‡
Exon 2	c.16T > G	p.Y6D	DD-II
Exon 2	c.44C > T	p.A15V	DGI-II
Exon 2	c.49C > A	p.P17T	DGI-II
Exon 2	c.49C > T	p.P17S	DGI-II
Intron 2	c.52-3C > G	p.V18_Q45del	DGI-II
Intron 2	c.52-3C > A	p.V18_Q45del	DGI-II
Exon 3	c.52G > T	p.V18_Q45del	DGI-II
		or p.V18F	DGI-III
			DGI-III
			DGI-II
Exon 3	c.133C > T	p.V18_Q45del	DGI-II
		or p.Q45X	
Intron 3	c.135 + 1G > A	p.V18_Q45del	DGI-II
Intron 3	c.135 + 1G > T	p.V18_Q45del	DGI-II
Exon 5	c.1870_1873 delTCAG	p.S624TfsX687	DD-II
Exon 5	c.1918_1921 delTCAG	p.S640TfsX671	DD-II
Exon 5	c.2040delC	p.S680fsX1313	DGI-II
Exon 5	c.2272delA	p.S758AfsX554	DGI-II
Exon 5	c.2525delG	p.S842TfsX471	DGI-II
Exon 5	c.2593delA	p.S865fsX1313	DGI-II
Exon 5	c.2684delG	p.S895fsX1313	DGI-II
Exon 5	c.3141delC	p.S1047fsX223	DD-II
Exon 5	c.3438delC	p.D1146fsX1313	DGI-II
Exon 5	c.3546_3550 delTAGCAinsG	p.D1182fsX1312	DGI-II

*The A of the ATG codon is taken as nucleotide 1 from reference sequence NM_0142083.
†These are predictions and have not been verified at the protein level.
‡Referenced in 14, 31.

Hereditary gingival fibromatosis

Gingival overgrowth, a benign enlargement of the gingiva, may occur as an isolated clinical finding (hereditary gingival fibromatosis; HGF), in association with additional clinical anomalies as part of a syndrome (syndromic gingival fibromatosis) or as a side effect of certain medications (drug induced gingival overgrowth) (3, 15). There is a genetic basis to the etiology of all three forms of gingival overgrowth. HGF is most commonly transmitted as an autosomal dominant trait. The condition may be moderate or severe in its clinical presentation, with gingival tissues covering the crowns of teeth, preventing normal eruption and leading to malocclusion, difficulty eating and speaking and esthetic concerns. Genetic studies of families segregating HGF have determined that the condition is genetically heterogeneous, with at least four different genes mapped (16–19). Studies of a large Brazilian family segregating HGF localized the responsible gene to chromosome 2 and identified a son of sevenless-1 (*SOS-1*) gene mutation as etiologic (16). A deletion mutation introduces a premature stop codon in the *SOS-1* coding sequence. This mutation creates a truncated SOS-1 protein which is more active than wild-type SOS-1 protein. SOS-1 is functionally important in signal transduction, controlling whether cells grow, differentiate or divide (OMIM182530) (1). SOS-1 is expressed by many cell types in many tissues. An intriguing question is why this disruption of such an important gene only affects the gingiva, leading to gingival overgrowth. Immunohistochemistry studies demonstrate that SOS-1 expression is much higher in gingiva than other types of skin. This highlights the uniqueness of many oral tissues and structures including enamel, dentin and gingiva. Dental tissues are unique in part due to unique patterns of gene expression.

Studies of gingiva from individuals with HGF show increased amounts of collagen, increased numbers of fibroblasts, and increased rates of fibroblast proliferation (20). Studies also demonstrate specific changes in fibroblast signal transduction associated with the *SOS-1* mutation in HGF patients (21). Mutant *SOS-1* can translocate to the plasma membrane without growth factor stimulation, leading to sustained activation of RAS/MAPK signaling. The resulting increase in the magnitude and duration of ERK signaling and increased phosphorylation of certain proteins in the nucleus is associated with the up-regulation of cell cycle regulators and transcription factors which promote cell cycle progression from the G(1) to S phase. These findings illustrate the mechanism by which mutant *SOS-1* causes HGF.

Findings of *SOS-1* related HGF illustrate clinical implications of genetic studies of diseases. Genetic studies of families segregating HGF enabled investigators to identify the etiologic gene responsible for the condition, providing a basis for genetic testing. Identification of the responsible gene provided a starting

point to understand how the *SOS-1* gene mutation causes gingival fibromatosis. This provides an understanding of the biological systems involved in development of HGF, and provides a rationale basis to consider development of treatment intervention strategies. Ultimately this kind of information increases our fundamental understanding of gingival development and may help develop tissue engineering strategies designed to repair damaged gingiva.

While the *SOS-1* gene mutation is etiologic for some cases of HGF, other cases of gingival fibromatosis are due to other types of genetic changes including chromosomal anomalies (3). Genetic studies of additional HGF families clearly indicate genetic heterogeneity. This means that mutations of additional genes can also cause HGF. As additional HGF causing genes are identified and their mechanism of action understood, researchers will develop a better understanding of gingival development that should facilitate development of better strategies to treat gingival diseases.

Papillon-Lefèvre syndrome

Papillon-Lefèvre syndrome (PLS) is characterized by plamar-plantar hyperkeratosis and severe, early onset periodontitis (OMIM245000) (1, 22). Affected individuals manifest severe gingival inflammation soon after the primary teeth erupt. Severe periodontitis develops with destruction of the periodontium. The primary teeth are prematurely exfoliated, and the gingival inflammation resolves until eruption of the secondary dentition, when the process of inflammation and destruction of the periodontium begins again. PLS is transmitted an autosomal recessive trait. Genetic studies localized the gene for PLS to chromosome 11, and subsequently cathepsin-C (*CTSC*) gene mutations were determined to be etiologic (22). CTSC is a proteinase, which functions to remove dipeptides from the terminus of protein substrates. *CTSC* is expressed in many tissues and cells, particularly neutrophils. *CTSC* is also highly expressed in the gingiva and skin on the palms and soles. More than 70 different *CTSC* mutations have been identified. These mutations span the entire gene and are found in highly conserved regions of the protein. Conservation of amino acids across species indicates that the conserved amino acids are functionally important. Specific mutations in highly conserved regions of cathepsin-C disrupt the enzymatic function of the protein (23, 24).

As cathepsin-C mutations associated with PLS cause the CTSC protein to lose its enzymatic activity, genetic testing for PLS may be performed by direct sequencing of the *CTSC* gene or by determining CTSC enzyme activity (Fig. 3) (25). Basic research has determined that cathepsin-C activity is needed to activate several important enzymes produced by neutrophils, called neutrophil derived serine proteases (NSPs). The NSPs cathepsin-G, elastase and proteinase 3 are secreted in an inactive, proenzyme form. Active cathepsin-C is needed to cleave the NSP propeptides and activate them. Neutrophils from PLS patients with *CTSC* mutations do not have active cathepsin-C and cannot activate the NSPs (26). Additional studies have determined that one of the biological molecules released at sites of inflammation is the chemokine macrophage

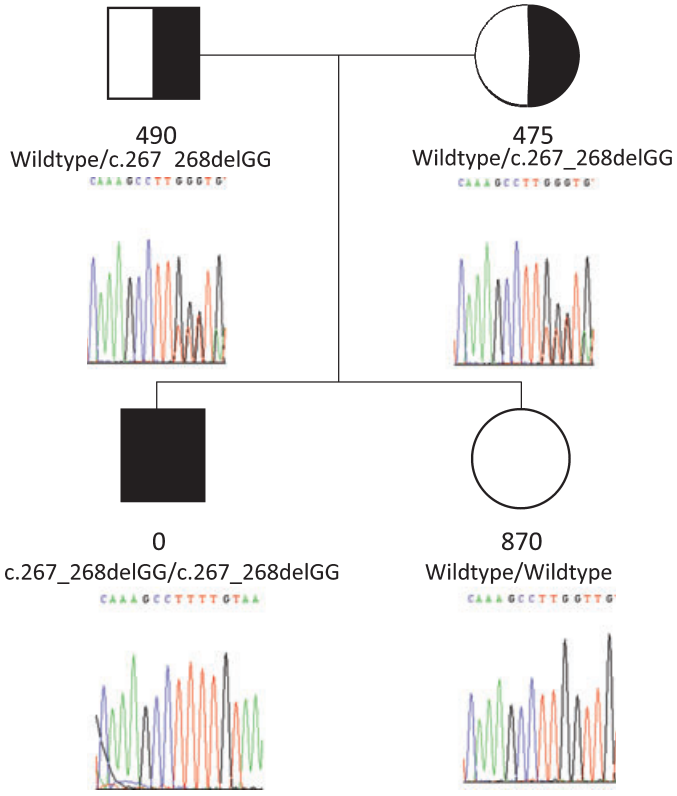


Fig. 3. PLS pedigree illustrating phenotype, *CTSC* genotype and CTSC enzyme activity. Filled symbols indicate individuals with a clinical diagnosis of PLS. Half shaded and open symbols are carriers and non-carriers, respectively, based upon biochemical and/or mutational analyses. The CTSC protease activity (μmol/min/mg protein) in leukocytes is given below each individual. Mutated *CTSC* alleles associated with PLS have no enzyme activity. Heterozygote individuals demonstrate approximately 50% enzyme activity levels found in individuals with 2 normal *CTSC* alleles. The affected individual is homozygous for a c.267_268delGG mutation.

inflammatory protein-1 alpha (MIP-1α). Inflammatory factors including microbial lipopolysaccharides (LPS) and the proinflammatory cytokine interleukin -1β that are associated with microbial plaque and inflammation in the gingival crevice induce MIP-1α expression by epithelial cells lining the gingival sulcus (27). Active NSPs are needed to regulate MIP-1α activity. Since PLS patients do not have active NSPs, they cannot regulate MIP-1α activity. Incorporating findings from several studies that have characterized the function of normal and mutant *CTSC*, we developed a model that may explain, in part, the mechanism by which *CTSC* mutations are etiologic for severe periodontitis. Severe periodontal destruction seen in PLS may result from a localized dysregulation of the inflammatory response (27). In this pathogenesis model, microbial plaque in the gingival crevice produces proinflammatory molecules such as microbial LPS that trigger a localized inflammatory response. Production of additional proinflammatory molecules is chemotactic for PMNs which invade the gingival crevice and the surrounding periodontium. MIP-1α, one of the many proinflammatory cytokines and chemokines produced at sites of inflammation, is a powerful chemoattractant for the continued influx of PMN. Normally, MIP-1α is cleaved and inactivated by the NSPs. As PLS patients can not produce active CTSC they cannot activate the NSPs and therefore cannot inactivate MIP-1α. Consequently, the recruitment and activation of additional PMNs cannot be regulated at sites of periodontal inflammation. Accordingly, PMNs continue to infiltrate the periodontium, enhancing the proinflammatory cascade, leading to the destruction of periodontal soft tissues and bone. Cathepsin-C mutations have also been associated with pre-pubertal periodontitis and aggressive periodontitis, indicating a role in other forms of periodontitis (28, 29).

Clinical implications and applications

A primary focus of biomedical research is directed at utilizing genetic information and technology to improve our understanding of genetic diseases to improve clinical care. Table 2 illustrates several of the numerous studies that have successfully identified the genetic basis of diseases of dental importance. It is important to consider how we can use genetic information to help diagnose and treat patients (Fig. 1). Identifying the genetic basis of a disease enables clinicians and scientists to understand the genetic underpinnings of disease and facilitate development of diagnostic tests. Diagnostic testing may be based on identification of mutations affecting specific genes such as those listed in Table 2. In addition to DNA based testing, other types of tests may be applied, such as biochemical testing for CTSC activity in PLS (Fig. 3) (25), and cytogenetic testing to identify chromosomal anomalies associated with syndromic forms of HGF such as Zimmerman-Laband syndrome (OMIM135500) (1). The ability to correctly diagnose a clinical disease also permits development of better nosology. Being able to identify individuals with similar forms of disease permits evaluation of treatments in individuals with shared disease etiology (Fig. 1). Ultimately an important goal is to develop proactive, preventative treatments, whereby susceptible individuals can be identified before the onset of disease, and intervention strategies employed to prevent development of clinical disease.

Genetic diseases from a public health perspective

As the genetic etiologies of diseases are increasingly understood, dentists must consider how this information can be used to improve patient care. Treatment of genetic diseases poses unique challenges to traditional treatment paradigms. For millennia, infectious diseases were responsible for significant human morbidity and mortality. Through research efforts, the etiology of significant infectious diseases affecting the US population, such as smallpox, diphtheria, measles and paralytic poliomyelitis, were identified, and etiology based treatment strategies developed. Once the infectious agents for these diseases were identified, and vaccines developed, the number of cases in the USA decreased dramatically. As a consequence, by the late 1990s the morbidity and mortality associated with these conditions virtually disappeared in the USA.

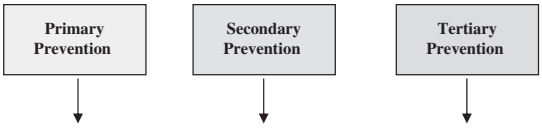
From a public health perspective, treatment of infectious diseases can be broadly considered at three levels of intervention [See Fig. 2; Hart et al. 2000 (30)]. To illustrate an infectious disease prevention paradigm, consider a more recent public health challenge, human immunodeficiency virus (HIV) infection. Untreated, individuals infected with HIV usually develop the clinical disease acquired immune deficiency syndrome

Table 2. **Summary of genetic diseases with genes identified as etiologic for each**

Clinical disease	Etiologic Gene/OMIM*	Chromosomal location of gene
Amelogenesis imperfecta	Enamelin (*ENAM*) OMIM606585	4q21
	Kallikrein 4 (*KLK4*) OMIM603767	19q13.4
	Matrix Metalloproteinase 20 (*MMP20*) OMIM604629	11q22.3-q23
	Family with sequence similarity, member H (*FAM83H*) OMIM611927	8q24.3
	Amelogenin (*AMELX*) OMIM300391	Xp22.3-p22.1
Dentinogenesis imperfecta	Dentin sialophosphoprotein (*DSPP*) OMIM125485	4q21.3
Osteogenesis imperfecta/ dentinogenesis imperfecta	Collagen type1 A1 (*COL1A1*) OMIM120150	17q21.31-q22
Osteogenesis imperfecta/ dentinogenesis imperfecta	Collagen type1 A2 (*COL1A2*) OMIM120160	7q22.1
Papillon Lefèvre syndrome	Cathepsin C (*CTSC*) OMIM602365	11q14.1-q14.3
Hereditary gingival fibromatosis	Son of sevenless-1 (*SOS-1*) OMIM182530	2p22-p21

*Online Mendelian Inheritance in man catalogue number (1).

(AIDS). Untreated individuals with AIDS develop complications including opportunistic infections. Public health efforts for infectious diseases are based upon identification of the etiologic infectious agent, and prevention of individuals becoming infected. Primary prevention is directed at preventing individuals becoming infected. For individuals already infected, treatment is directed at secondary prevention, controlling the onset of clinical disease, such as with antiretroviral treatments. Before such treatments were available, treatment was directed at tertiary prevention, controlling complications of the clinical disease. Ultimately successful treatment is based on the ability to identify and understand the etiologic basis of a disease. For infectious diseases, treatment prevention strategies are directed at preventing infection: by avoiding infection or by enabling the host to effectively overcome the infectious challenge such as with vaccines. When a disease is not understood, palliative care and tertiary prevention are usually the only treatment possible. As the disease is understood, secondary prevention can be directed at controlling clinical disease.



Simple Mendelian Trait	Genotype mutation	Clinical Disease	Clinical Complications
Dentinogenesis Imperfecta	*DSPP* OMIM 125485	Defective dentin	Enamel fracture Dental abscess Poor esthetics Nutritional compromise
Amelogenesis Imperfecta	*ENAM* OMIM606585 *KLK4* OMIM603676 *MMP20* OMIM604629 *FAM83H* OMIM611927 *AMELX* OMIM300391	Defective enamel	Tooth pain/sensitivity Dental abscess Poor esthetics Nutritional compromise
Papillon-Lefèvre syndrome	*CTSC* OMIM602365	Severe periodontitis Palmar-plantar hyperkeratosis	Premature tooth loss Oral Pain Nutritional compromise Painful skin lesions hands and feet

Disease Prevention Paradigm for Mendelian Genetic Traits

Fig. 4. Disease prevention paradigm for Mendelian diseases. Mendelian diseases reviewed in text are listed in the left column. Specific gene(s) for which etiologic mutations have been identified for each condition are listed in the second column, with the associated Online Mendelian Inheritance in Man (OMIM) catalogue number (1). Third column lists primary pathologic findings associated with mutations of each gene. Fourth column lists clinical complications that commonly result due to the underlying disease pathology. Possible points of treatment intervention (primary, secondary and tertiary) are indicated above.

Primary prevention is the most effective, but is predicated on understanding the etiologic basis of disease (30).

Disease prevention paradigm for a Mendelian genetic disease

When considering genetic diseases, we must reconsider prevention strategies, as it is not usually possible to prevent individuals inheriting disease genes. Figure 4 illustrates the case for several of the Mendelian diseases we have discussed. Improving treatment beyond tertiary prevention will depend upon our ability to correctly diagnose the etiologic form of disease and to understand each disease sufficiently to permit identification of biologic targets for treatment to overcome the primary genetic defect (30).

Clinical relevance

Clinical and basic research has identified the genetic basis for many diseases of dental importance. Findings from these studies provide a basis for improved diagnosis, classification and treatment of diseases. The dental community must consider how to incorporate these developments into effective disease prevention paradigms to facilitate the diagnosis and treatment of individuals with genetic diseases.

Acknowledgements: The authors were supported by the Intramural Research Programs of the National Institute of Dental and Craniofacial Research (Z01-DE000711) and the National Human Genome Research Institute of the National Institutes of Health, Bethesda, MD. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Dental and Craniofacial Research, the National Human Genome Research Institute or the National Institutes of Health.

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