



# Inherited Dental Anomalies: A Review and Prospects for the Future Role of Clinicians

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**ABSTRACT** Inherited dental anomalies such as hypodontia, supernumerary teeth, enamel defects, and diastema are evident in large segments of most populations. Although treatment options for many of these conditions are ever improving, much remains to be understood about their etiology and pathophysiology. In this review, the authors hope to entuse dental professionals into aiding the human geneticist by collaborating in studies seeking the underlying genetic cause of dental anomalies and referring patients presenting these conditions to the human geneticist.

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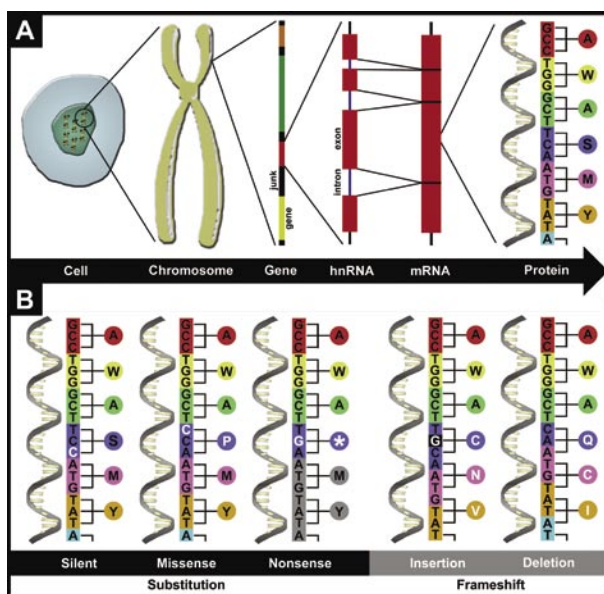
As the oral health of the population improves, considerations are now turning toward cosmetic dentistry, and the prospect of a complete and well-maintained set of dentition is within the reach of many more individuals. The correction of malpositioned and crowded teeth, as well as tooth discoloration and shape, are becoming ever more common. However, the knowledge of treatment techniques for these conditions is far more extensive than the understanding of their genetic basis. Numerous diseases of the dentition have been identified that lead to unfavorable changes in the affected person's dentition. These include hypodontia, supernumerary teeth, and alterations due to enamel defects.<sup>1-4</sup> While genetic factors underlying some of these conditions

have been identified, the vast majority remain only partially understood.<sup>5-13</sup>

Dental anomalies are ideal conditions for the human geneticist to study as they are well-suited to the identification of the hereditary factors involved in their pathogenesis. While most dental anomalies can severely impact the quality of life in patients, they are not fatal. This provides a multigenerational family structure for genetic studies into their underlying causes. The problem for human geneticists is in the recruitment of families within which these diseases track. Most dental professionals, unlike medical professionals, are situated away from the human geneticist, hindering collaboration.

The authors review here the current understanding of the genetic basis of dental anomalies for which a gene or locus has been identified as the cause of the disorder, and highlight the fact

**FIGURE 1.** From gene to protein. (A) Chromosomes are found in the nucleus of the cell. Comprised of DNA, these chromosomes contain thousands of genes (colored blocks), which are separated by noncoding, or "junk," DNA (black blocks). Each gene is comprised of both exons (coding DNA; red) and introns (noncoding DNA; blue), which are copied or transcribed (expressed), for the purposes of constructing the protein it codes for, or encodes. There is an intermediary stage between the gene and the protein where a temporary copy of the gene blueprint is produced as a heterogeneous ribonucleic acid molecule, or hnRNA. The hnRNA consists of both the exons, which are pieced together to form the messenger RNA, or mRNA, and the introns, which are discarded. The mRNA is used as the template for the synthesis of the protein from amino acid building blocks. For this, the DNA is read in three-letter



blocks, called codons, each of which signifies a single amino acid (colored circles). (B) The five major types of mutation. Silent mutations cause no change in the encoded amino acid sequence due to redundancy in the codons. Missense mutations lead to a single change in the encoded amino acid sequence. Nonsense mutations result in the formation of one of the three translation stop codons (TAA, TAG, and TGA) that result in truncation of the encoded amino acid sequence. Frame-shift mutations (insertions or deletions) result in a change in the encoded amino acid sequences from the point of the mutation as they shift the nucleotide positions in each triplet codon such that they form different codons. The mutated nucleotide and the affected amino acids are shown in white. \* indicates the position of a stop codon.

that there remain many opportunities for further discovery. The authors hope this will stimulate the dental professional to collaborate with the human geneticist and facilitate the recruitment of families afflicted with dental anomalies into genetic mapping studies.

### Primer in Human Genetics

The complete DNA content of a human cell, its genome, is currently thought to encode 20,000-25,000 genes, the discrete units of information stored in the genome, spread over 22 pairs of autosomal chromosomes and a pair of sex chromosomes (the X and the Y chromosomes) within the nucleus of all 10 cells that make up the human body.<sup>13,14</sup> Each gene acts as the blueprint for the synthesis of a protein that once produced, performs tasks within the cell. This multistage synthesis process is summarized in **FIGURE 1A**. Subtle changes in the DNA of these genes, mutations, between one individual and another define each of us as different. The

most common type of mutation in DNA is a single nucleotide polymorphism (**FIGURE 1B**), of which a vast majority are silent and cause no visible or phenotypic consequences. However, should a nucleotide substitution cause a change at a location that results in an altered protein product that does not function appropriately or in the gene's control elements that can result in it not even being synthesized, the cells containing that genetic change may no longer perform their normal function, leading to a disease state.

Molecular genetics is essentially the study of these defective genes as they pass from one generation to next by the process called inheritance, thereby determining hereditary traits, such as the color of one's hair or eyes. Mutations can either be inherited from a parent, in which case they will be present in all cells of the body, or they can be acquired during an individual's lifetime, where they could be restricted to a particular part of the body depending upon when during the development of

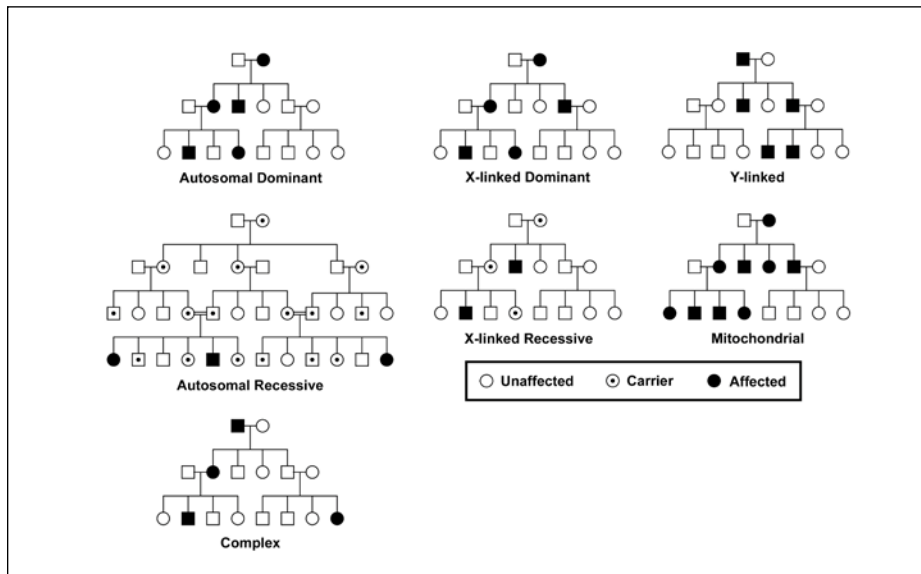
the individual the mutation was acquired. The former can be passed through families in a variety of Mendelian (single causative gene; autosomal/X-linked dominant or recessive) or complex (multiple causative genes) inheritance patterns (**FIGURE 2**).

The human geneticist identifies the disease gene(s) and its associated mutation(s) using a process called linkage analysis. This process, summarized in **FIGURE 3**, uses genetic markers that are known to have more than one form in the genomes of the population to identify regions of the genome that are associated with the disease in the affected family. This is achieved by sifting through many of these markers spread throughout the genome looking for those that are only found in one particular form in affected but not unaffected family members. The region(s) identified can then be analyzed to find the gene and mutation responsible for the disease, most commonly by sequencing the protein-coding parts of the gene(s) in the region(s).

As the knowledge is expanded of the genetic basis of diseases affecting the human population, it is becoming increasingly evident that many follow a complex rather than Mendelian pattern of inheritance. As these complex diseases require larger populations of affected individuals for the successful identification of their underlying genetic causes, they present a problem to the human geneticist. The identification of individuals afflicted with the condition and their referral into these genetic studies is reliant upon the clinician. As human geneticists largely reside away from the clinician, they can sometimes be unaware of the human geneticists' studies and thus not refer their patients. For dental anomalies, this is even more acute as dental professionals practice within urban areas away from

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## ANOMALIES, CONTINUED FROM 326



**FIGURE 2.** Idealized patterns of inheritance in pedigree diagrams. Autosomal dominant inheritance shows both males and females affected through successive generations with one-half of all offspring affected, and can be distinguished by male-to-male transmission. Autosomal recessive inheritance also shows both males and females affected, but affecteds are normally just present in a single generation where one-fourth of all offspring are affected and the parents of these offspring are often blood relatives. X-linked dominant inheritance also affects both males and females in successive generations with one-half of all offspring at risk (i.e., a parent is a carrier) affected, but can be distinguished by the lack of male-to-male transmission. X-linked recessive inheritance has affected males but generally only carrier females (i.e., females who have one copy of the disease gene but do not present the condition), unless an affected male marries a carrier female from which females with two copies of the disease gene can occur. Nonsuccessive generations will be affected with one-half of males being affected and one-half of females being carriers. Y-linked inheritance will be passed from male to male through successive generations and can be distinguished by no affected females and no female-to-offspring transmission. Mitochondrial inheritance shows only affected females transmitting the disease to all offspring; no male-to-male transmission occurs. Finally, complex inheritance shows both affected males and females, but with no discernible pattern or frequency.

the major genetics institutes, hindering collaboration between both parties.

### Hypodontia

Hypodontia has been classified into two classes: syndromic, where tooth agenesis is found within individuals who have an underlying recognizable clinical syndrome, or nonsyndromic, where tooth agenesis is the primary condition afflicting the individual. Some syndromic conditions that present hypodontia have had genes identified as their cause, but only the genes identified as a cause of Rieger syndrome and Wolf-Hirschhorn syndrome appear to have functions that could putatively result in hypodontia when altered.<sup>15,16</sup>

Rieger syndrome (OMIM 180500),

which is characterized by hypodontia, malformation of the anterior chamber of the eye and a protuberant umbilicus, was initially linked to the short arm of chromosome 4 (4q25-q27) in 1992.<sup>17-19</sup> Further mapping refined the region within which the gene mapped. Sequencing of candidate genes resulted in the identification of six mutations in the homeobox transcription factor gene *PITX2* (OMIM 601542), with others subsequently identified.<sup>20-22</sup> As murine *Pitx2* expression is restricted to the dental epithelium during tooth development, it represents the most likely candidate for the cause of the hypodontia presented in Rieger syndrome patients.<sup>20,22</sup> Another locus on the short arm of chromosome 13 (13q14) has also been associated with Rieger syndrome in

families that do not show association with 4q25, indicating that this condition may be caused by multiple factors, although no gene has yet been identified at 13q14.<sup>23</sup>

Wolf-Hirschhorn syndrome (WHS; OMIM 194190), which is characterized by profound mental retardation, heart defects, and facial clefting, was associated with the deletion on the long arm of chromosome 4 in 1965.<sup>24,25</sup> In 1989, it was shown that deletion of the 4p16.1 locus was sufficient to cause WHS and that deletion of the homeobox gene *MSX1* (OMIM 142983), which is located at 4p16.1, also led to WHS.<sup>26,27</sup> Oligodontia was found associated with WHS in seven Finnish patients, of which five were subsequently shown to have a deletion of one *MSX1* gene, leading to the conclusion that haploinsufficiency for *MSX1* serves as a mechanism that causes selective tooth agenesis and WHS.<sup>28</sup>

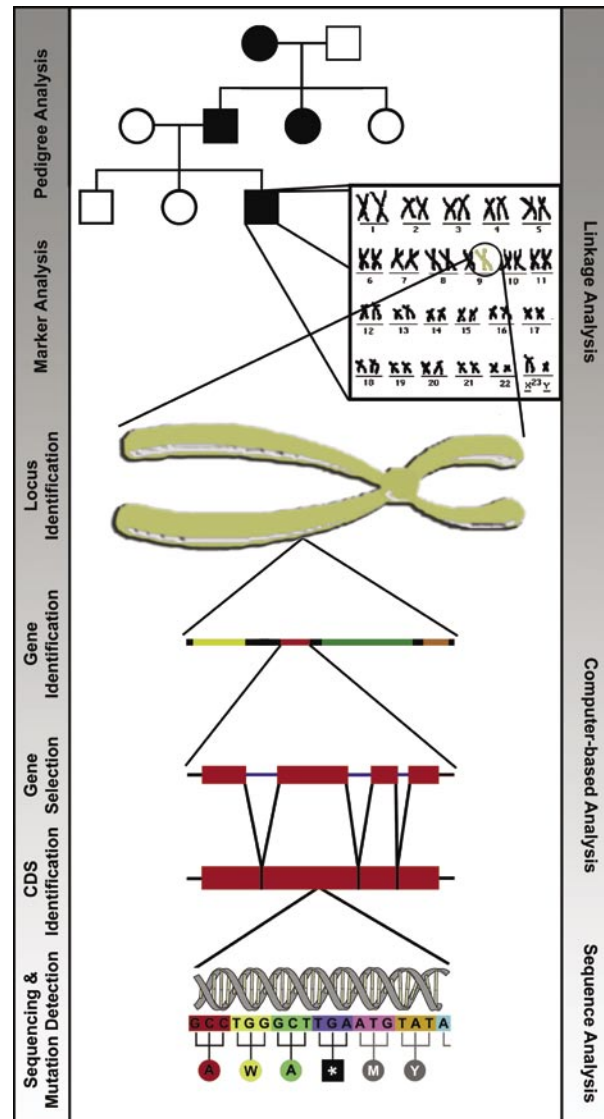
Genetic association studies into nonsyndromic hypodontia have so far identified three genes underlying this condition in numerous families: *MSX1* (OMIM 142983), *PAX9* (OMIM 167416) and *AXIN2* (OMIM 604025). Genetic linkage analysis of a family with autosomal dominant agenesis of second premolars and third molars identified a locus on the long arm of chromosome 4 (4p16.1) where sequence analyses demonstrated a mutation in the homeodomain (DNA-binding domain) of *MSX1* gene in all affected family members.<sup>6</sup> It was believed this mutation perturbed the ability of *MSX1* to interact with its DNA or protein binding partners leading to haploinsufficiency of *MSX1* in affected individuals. Subsequent research into other families afflicted with hypodontia has identified five other mutations in *MSX1*.<sup>9,29-31</sup> It appears likely that disruption of *MSX1* functioning serves as a mechanism that causes selective tooth agenesis.

*PAX9* was first associated with hypodontia in 2000 after the association of a locus on the short arm of chromosome 14 (14q12) during genetic linkage analysis of a family lacking most of their permanent molars.<sup>8</sup> The gene *PAX9* was found to be localized in this region of chromosome 14, and it was selected as a candidate gene based upon the observation that mice engineered to completely lack *Pax9* lacked teeth.<sup>32</sup> A single nucleotide insertion that resulted in a frame-shift mutation was then identified within its sequence.<sup>8</sup> Subsequent research has identified other mutations within its sequence that link it to hypodontia that range from single nucleotide substitutions or insertions to the deletion of the entire gene.<sup>33-40</sup> It appears it is the disruption of the DNA-binding ability of *PAX9* that causes hypodontia.

*AXIN2* was associated with oligodontia in 2004 after genetic linkage analysis of a Finnish four-generation family suffering from severe autosomal dominant oligodontia with sporadic colorectal neoplasia.<sup>41</sup> A region containing 80 genes on the short arm of chromosome 17 (17q24) was identified as associated with the oligodontia in this family. *AXIN2* was selected based upon previous research into colorectal cancer and sequence analysis identified two separate mutations in affected individuals. Both were single nucleotide substitution mutations that resulted in truncation of the protein product.<sup>41</sup> It therefore appears that loss of *AXIN2* function results in oligodontia and in some patients, also colorectal cancer.

### Hyperdontia

Hyperdontia (also referred to as supernumerary teeth; OMIM 187100), like hypodontia, can be classified into two classes: syndromic and nonsyndromic. Relatively recently there was success in determining a genetic cause for cleidocra-



**FIGURE 3.** Methodology of disease gene and mutation identification. A pedigree (family tree) of the afflicted family is first drawn to identify the mode of inheritance of the disease trait (autosomal dominant or recessive, X-linked dominant or recessive, Y-linked, mitochondrial or complex). Linkage analysis is then performed using genetic markers (microsatellites or SNPs) to identify the region(s) of the chromosome(s) associated with the disease. Genes in the associated region(s) are then identified using sequence repositories available through the Internet and then candidate genes are selected based upon their known or predicted functions. Sequence analysis of these candidate genes will hopefully reveal a mutation in their coding sequence (CDS) that is present in all affected but not unaffected individuals and thus is probably the cause of the disease.

nia dysplasia (CCD; OMIM 119600), an autosomal-dominant condition characterized by hypoplasia/aplasia of clavicles, patent fontanelles, supernumerary teeth, short stature, and other changes in skeletal patterning and growth, in multiple families afflicted with CCD.<sup>42</sup> After association was found with a region on the short-arm of chromosome 6, *CBFA1* (also called *RUNX2*; OMIM 600211), a member of the runt family of transcription factors and a critical transcriptional regulator of osteoblast differentiation, was found to contain mutations ranging from dele-

tions resulting in heterozygous loss of the gene to insertion, deletion, and missense mutations leading to translational stop codons in the DNA binding domain or in the C-terminal transactivating region of the protein, both of which are important for the functioning of the protein.<sup>42-47</sup> Mutagenesis of the mouse *Cbfa1* gene have produced phenotypes that show a high degree of homology to CCD and showed that *Cbfa1* is a mesenchymal-factor required for correct epithelial-mesenchymal interactions regulating tooth development.<sup>48,49</sup> Interestingly, the teeth

in mice lacking *Cbfa1* failed to advance beyond the bud stage, and the mandibular molar organs were more severely affected than maxillary molar organs.<sup>50</sup> It appears likely that *CBFA1* mutations cause CCD and that haploinsufficiency is sufficient to produce this disorder, but how decreasing levels of *CBFA1* can lead to either supernumerary teeth or failed tooth development still remains unknown.

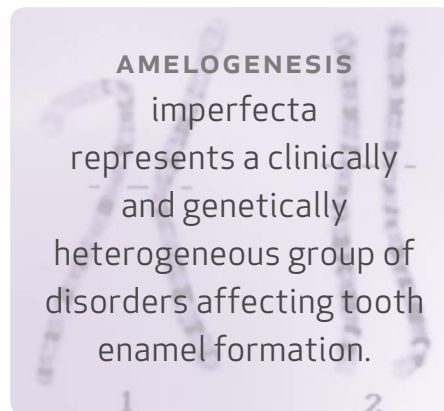
However, despite this success, there have been no other reported cases where the cause of nonsyndromic hyperdontia has been identified. The small-eye mutant phenotype in mice, which includes the possession of supernumerary teeth, has been shown to have arisen from defects within the *Pax6* gene, a member of the paired-domain transcription factor family of proteins that includes *Pax9*, which the authors discussed as a known cause of hypodontia.<sup>51</sup> But there have been no human association studies reported.

### Amelogenesis Imperfecta

Amelogenesis imperfecta represents a clinically and genetically heterogeneous group of disorders affecting tooth enamel formation. Enamel is formed by mineralization of an extra cellular matrix that contains proteins secreted primarily by ameloblasts.<sup>52</sup> Approximately 90 percent of the organic matrix protein is amelogenin, which is expressed differentially from two genes, *AMELX* (OMIM 300391) and *AMELY* (OMIM 410000).<sup>53,54</sup> It had been hypothesized that altered amelogenin function may be associated with AI.<sup>55</sup> The first mutation supporting this hypothesis was reported in 1991 with the partial deletion of the *AMELX* gene found in a Swedish family whose condition was associated with the region on the X-chromosome where the *AMELX* gene is located.<sup>5</sup> Since then, 13 other reported mutations in

the *AMELX* gene have been identified, which is surprising considering less than 5 percent of AI cases are X-linked, but, interestingly, no mutations have yet been reported in the *AMELY* gene.<sup>56-68</sup>

Enamelin (ENAM; OMIM 606585) represents between 1 percent and 5 percent of total matrix protein content with proteolytic processing giving rise



to multiple ENAM isoforms.<sup>69-72</sup> In 1997, a locus for autosomal dominant AI was mapped to chromosome 4 (4q11-q21) using six Swedish families.<sup>52</sup> The human chromosomal localization of *ENAM* was subsequently identified as 4q13.1-q21.23, and, in 2001, a mutation in the *ENAM* gene was finally identified in a family presenting autosomal-dominant AI.<sup>12,73</sup> Since the initial discovery, four more *ENAM* mutations have been identified, three for autosomal dominant and a single for autosomal recessive AI.<sup>13,68,74,75</sup>

*DLX3* (OMIM 600525), mapped to human chromosome 17 (17q21.3-q22), is a member of the distal-less family of homeodomain transcription factors, and it has been implicated in the control of tissue differentiation.<sup>76-79</sup> It has previously been found to be a cause of Trichodentosseous Syndrome (presented later), but

in 2005 the cause of autosomal dominant hypoplastic-hypomaturational AI with taurodontism presented by a family was associated with the region containing *DLX3*.<sup>80</sup> *DLX3* was subsequently sequenced and a two-nucleotide deletion was identified within its homeodomain (DNA-binding domain) that led to a frameshift that altered the protein product.<sup>80</sup>

Finally, an enamel-specific protease has recently been identified as a cause of rare autosomal recessive hypomaturational AI. Kallikrein-4 (*KLK4*; chromosome 19q13.3-q13.4; OMIM 603767) is expressed during the maturation stage as the enamel hardens.<sup>81</sup> A nonsense mutation was identified in the affected members of a family afflicted with this form of AI during the sequencing of candidate genes in the region identified by linkage analysis.<sup>82</sup>

### Trichodentosseous Syndrome

Trichodentosseous syndrome (TDO; OMIM 190320) exhibits autosomal dominant inheritance of enamel hypoplasia and hypocalcification, and taurodontism with associated strikingly curly hair.<sup>83</sup> Further analysis has since shown that two of the clinical features, taurodontism and enamel hypoplasia, were fully penetrant in all affected individuals, while bone and hair features were variably expressed, indicating that their cause may be complex rather than Mendelian.<sup>84</sup> The genetic cause of TDO was first associated with a region on the short arm of chromosome 17 (17q21) in 1997 after genetic linkage analysis of four families with a total of 39 affecteds.<sup>85,86</sup> Two candidate genes of the distal-less homeobox gene family, *DLX3* and *DLX7*, were selected based upon murine studies that highlighted their important role in the development of hair, teeth, and bone. The following year, Price et al. published the identification of a mutation in the *DLX3* gene (OMIM

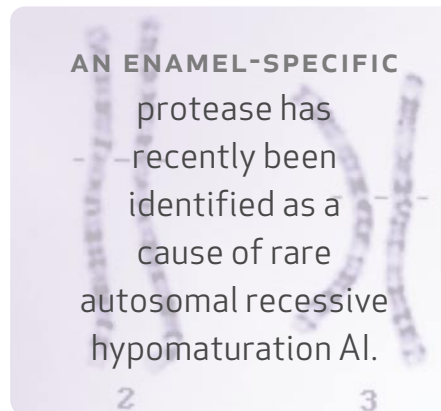
600595) as the cause of TDO in these families with it likely causing haploinsufficiency of functional DLX3 protein.<sup>87</sup> It has also subsequently been shown that while amelogenesis imperfecta and TDO share similar characteristics, they are genetically distinct conditions.<sup>88</sup>

### Dentinogenesis Imperfecta

Dentinogenesis imperfecta (DGI; OMIM 125490) is an autosomal dominant inherited dental disease that affects dentin production and mineralization. It was first linked to a locus on the short arm of human chromosome 4 in 1982.<sup>89</sup> Several groups pursued fine-mapping and narrowed the interval to 4q21 by 1999.<sup>90-92</sup> This region curiously has a high proportion of genes encoding dentin and bone ECM proteins: secreted phosphoprotein 1 or osteopontin (*SPP1*), dentin matrix protein 1 (*DMP1*), matrix extracellular phosphoglycoprotein, bone sialoprotein II (*IBSP*) and *DSPP*, a gene encoding dentin sialophosphoprotein that is processed into two proteins: dentin sialoprotein (DSP) and dentin phosphoprotein (DPP).<sup>93</sup> Three of these genes (*DSPP1*, *IBSP* and *DMP1*) were excluded by linkage or mutation analysis as causes of DGI. *DSPP* was subsequently evaluated for mutations and since the initial identifications in 2001, many more mutations have been identified strongly linking loss of DSP and DPP function to the development of DGI. *DSPP* has also been associated with another dentine dysplasia, which could indicate it may be a predominant cause of these conditions.<sup>94-100</sup> Interestingly, a knock-out mouse that was lacking the gene encoding sphingomyelin phosphodiesterase 3 (*Smpd3*) presented a severe form of DGI, along with osteogenesis imperfecta, indicating that other genes may also underlie this condition.<sup>101</sup>

### Conclusions

The authors have discussed in this paper anomalies that are predominantly characterized by a Mendelian mode of inheritance caused by the disruption of a single gene. However, a majority of diseases and anomalies arise from a complex mode of inheritance where the disruption of multiple



genetic factors plays a part in causing the condition. These complex diseases are now being tackled with ever-increasing frequency but with varying degrees of success, largely due to the limited affected populations available to the human geneticist.

In every subspecialty of dentistry, genetic considerations are under scrutiny in the hope of improving therapy. It is known that tooth movement only progresses at the rate at which the density of bone and rate of bone resorption will allow. Limitations to such genetic correlation lie in the complexity of the multiple genetic processes that dictate bone quality. Implants, orthodontics, and oral surgery rely heavily on how well the clinician can predict the outcome of bone health after delivery of treatment options. Periodontitis,

for example, is caused by pathogenic bacteria common in plaque acting as a trigger point for its major underlying cause: a heightened and sustained inflammatory response. The complexity of the human inflammatory response and its obvious role in periodontitis has led both periodontists and scientists to consider the genetics underlying a person's predisposition to various forms of periodontal disease.<sup>102-107</sup> There has been some success in associating polymorphisms in certain interleukins with certain types of periodontal disease, which in some cases are isolated to certain subpopulations.<sup>104,106</sup>

It appears that in most cases discussed in this paper, it is the haploinsufficiency, or lack, of functional protein that leads these mutations to cause their associated phenotype. However, in many cases knowledge is still such that we do not know how the mutations cause this loss of function. As the reader will appreciate, compared to the number of known dental anomalies, the number for which we have some knowledge of their underlying genetic cause is extremely small. To identify the genetic basis of the remaining multitude of anomalies, the human geneticist requires families within which these anomalies are found to segregate. The dental professional is best placed to aid the human geneticist as in most cases they will treat complete families and can therefore identify whether a particular anomaly is found throughout the different generations. Should the dental professional find such a family, it is imperative to gain a complete family history and to create a family tree highlighting affected and unaffected members. Then through collaboration with the human geneticist, the underlying genetic cause can be identified. ■■■■

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