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The influence of genetics on oral health and disease: Current understanding and future direction

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Abstract

Our genes play a significant role in determining our oral health and susceptibility to dental diseases. This article explores the current understanding of how genetics influences oral health. It delves into how genes contribute to the development of various oral conditions, including caries (cavities), periodontal disease (gum disease), and oral cancer.

The article also discusses the latest advancements in using genetic information to improve oral healthcare. This includes potential applications in risk assessment, personalized prevention strategies, and the development of targeted therapies.

Looking towards the future, the article explores promising areas of research in oral genetics. It highlights the potential for genetic testing to revolutionize preventive dentistry and pave the way for more effective treatment approaches.

Keywords: Oral health; Genetics; Periodontal disease (gum disease); Targeted therapies

1. Introduction

Genetics is the scientific field dedicated to exploring genes, from their microscopic structure to their influence on entire populations. This field emerged in the early 20th century, and in the 1950s, scientists unraveled the building blocks of DNA, the molecule that stores our genetic information. The Human Genome Project further revolutionized genetics, revealing the vast number of genes present in each cell [1,2].

Pioneering work by Gregor Mendel established the principles of inheritance, which continue to be the foundation of genetics today. These principles explain how traits are passed down from parents to offspring [3].

Genetic variations can sometimes lead to health conditions. These variations can be very small, involving a single misplaced unit within the DNA code, or larger, affecting entire chromosomes. The information encoded in our genes

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directs the creation of proteins, the building blocks of our body. Any disruptions in this process can contribute to the development of diseases[4].

Recent advancements in genetics and related fields have opened doors to a new understanding of oral health. Researchers are now exploring the role of genes in various dental problems [5].

For decades, anecdotal evidence has suggested a link between family history and oral health issues. However, recent advancements in genetics are finally unveiling the intricate dance between our genes and the health of our smiles [6]. This review delves into the current understanding of how genetic predispositions interact with environmental factors to influence oral health, focusing on the most common conditions and exploring the potential of personalized oral care strategies.

2. Genetic Predispositions and Oral Health

Our genetic makeup, the blueprint of our physical being, plays a crucial role in oral health. Genome-wide association studies (GWAS) have identified numerous single nucleotide polymorphisms (SNPs) associated with various oral health conditions [7, 8]. These SNPs can influence various aspects, including:

- **Enamel Development:** Genes like ENAM (amelogenin) and MMP20 (matrix metallopeptidase 20) affect enamel structure and mineralization, impacting susceptibility to cavities
- **Saliva Composition:** Genes like MUC5B (mucin 5B) and DEFB1 (defensin beta 1) determine the composition of saliva, which plays a vital role in maintaining oral health by regulating bacterial growth and providing lubrication
- **Craniofacial Development:** Genes like MSX1 (muscle segment homeobox 1) and PAX9 (paired box 9) influence jaw development and tooth positioning, which can affect susceptibility to malocclusion (improper bite)
- **Immune Response:** Genes within the Human Leukocyte Antigen (HLA) complex influence the immune system's response to oral bacteria, impacting the risk of periodontal disease [9, 10].

2.1. Genetics and Oral Health

The human body contains 23 pairs of chromosomes, each with thousands of DNA gene sequences. Factors like time, environment, and cell type determine gene expression. Control of gene expression is essential for the proper growth, development, and functioning of an organism. Mendelian inheritance patterns involve children inheriting one chromosome from each parent, and depending on the dominance of a gene in those chromosomes, a particular trait or disease may develop in the child [11,12] .

Autosomal dominant inheritance requires only one chromosome in the pair to have the gene defect in question for the trait to manifest. Autosomal recessive inheritance requires one copy of the defective gene from each parent for the disease or disorder to occur. Sex-linked genes occur on either the X or Y chromosome, but only males can inherit Y-linked genes[13]. Chromosomal anomalies result from defects in chromosomes that involve multiple genes, leading to multiple physical defects, intellectual and developmental disturbances. Multifactorial inheritance/complex traits include diseases such as diabetes, hypertension, bipolar disorder, nonsyndromic cleft lip and/or palate, dental caries, and periodontal disease. Epigenetics refers to the mediation of gene expression without changes to the DNA sequence, which may account for phenotypic variation between monozygotic twins [14,15].

Traits can be discrete or continuous, and expression can be controlled by environmental exposures or modifier genes. Dominant genes may have variable expressivity creating a range of phenotypes, while penetrance refers to the likelihood of a gene variant arising in a phenotype. Environmental and other external and internal factors can affect the expression of one's genotype, so that the presence or absence of gene variants or alleles only partially affects one's phenotype [16,17].

Dental caries is caused by the acidic environment resulting from carbohydrate metabolism when sugars are introduced to the oral microbiome. The etiology of dental caries is complex and multifactorial, with genetic control and genes involved in the process being debated[18-20].Twin studies suggest partial genetic control, ranging from 20% to 85%. Early childhood caries experience may be strongly influenced by maternal health or obesity, and living in rural areas, low socioeconomic status, less frequent tooth cleaning, and sugar-containing soft drinks are associated with a higher prevalence of dental caries. Oral health awareness and hygiene practices, particularly fluoride exposure, may also mediate heritability of caries experience[21-25] .Most commonly associated genes with caries are involved with enamel formation and tooth mineralization, immune response, salivary characteristics, and taste. Amelogenin (AMELX) and

enamelin (ENAM) are responsible for tooth mineralization, while other genes may indirectly affect caries experience by modulating behavioral or metabolic factors, such as taste-receptor genes and the starch enzyme salivary amylase (AMY1), which has been associated with obesity [26].

Table 1 Genetics and Oral Health

Gene	Role	Associated Disease
Ameloblastin (*AMBN*)	Enamel matrix	caries
Amelogenin (*AMELX*)	Tooth mineralization	Amelogenesis imperfecta
Amylase Alpha 1 (*AMY1*)	Salivary starch digestion	caries
Aquaporin 5 (*AQP5*	*Saliva production*	Caries
Carbonic Anhydrase VI (*CA6*)	Saliva pH regulation	Caries
Enamelin (*ENAM*)	Enamel matrix	caries

2.2. Genetics and Plaque Microbiome

The plaque microbiome is largely hereditary and under significant genetic control in early life and emerging dentitions. However, environmental exposures throughout life increasingly affect the taxa present. Acidogenic Streptococci species are the most abundant pathogens in the oral environment, but the proliferation of cariogenic bacteria is primarily due to environmental exposure, such as the introduction of carbohydrate-rich foods[27]. Genetic control of the oral environment is likely responsible for healthy or non-cariogenic bacteria that make up plaque during dentition development. Predominant cariogenic taxa include Streptococcus mutans, S. sobrinus, and Lactobacillus spp. Recent studies suggest that Scardovia wiggsiae may also be associated with caries, particularly early childhood caries. Archaeological studies show that plaque microflora became less diverse and more dominated by cariogenic Streptococci after the transition to agriculture around 10,000 years ago and again after the Industrial Revolution [28,29].

2.3. Periodontal disease & genetics

Periodontal disease is a complex and multifactorial condition that is linked to overall health, with risk factors such as smoking and diabetes playing a significant role. It is believed to be caused by a combination of mechanisms, including the subgingival microbiome, genetic and epigenetic factors, behavioral and environmental factors, and systemic health. The disease is a two-step process, requiring both genetic susceptibility and a "bacterial challenge." Genetics plays a role in the etiology by controlling periodontal structural integrity and affecting the host response to subgingival microbiota. Heritability of the genetic control of periodontal disease is estimated at around 30% to 50%, with gene variants varying according to population [30]. The periodontal microbiome includes Porphyromonas gingivalis, Aggregatibacter actinomycetemcomitans, Tannerella forsthia, and Treponema denticola. The destruction from periodontal disease is largely driven by the host response to microbiotic dysbiosis, with immune response cytokines driving inflammation and the activity of matrix metalloproteinases (MMPs) responsible for tissue destruction. Most research into the genetic control of periodontal disease has focused on these regulatory and immune response mechanisms [31,32].

Caries and periodontal diseases are complex conditions with multiple genetic, behavioral, and environmental risk factors. Noninvasive salivary tests are available, but their clinical utility is limited due to the multifactorial etiology of these diseases. Candidate gene and GWAS studies have identified potential susceptibility loci for caries, such as enamel-formation genes, tooth development enzymes, and tooth development enzymes. Oral microbiota profiles may predict caries risk [33,34].

2.4. Genetic test

A genetic test for caries susceptibility has the potential to identify patients at risk prior to disease occurrence, but there is currently no genetic test with this predictive ability. There may also be opportunity to develop genetic tests to develop more targeted therapies that address an individual's personal risk [35].

The most reliable predictor of caries risk is the presence of at least one caries lesion, while other clinical risk indicators include a diet with frequent exposures to simple carbohydrates, poor oral hygiene, visible plaque, high levels of cariogenic bacteria, low socioeconomic status, and low oral health literacy. Genetic information about an individual's risk profile may change how disease is managed in the future [36].

Genetic testing for microbial identification may offer additional avenues for clinical application, such as identifying a basis for severe disease in young individuals or understanding drivers of inflammation in excess of local factors. Microbial testing may also provide insight for patient management when treatment responses are poor [37].

At this time, neither genotyping nor microbial testing are recommended as routine dental procedures to identify the presence, absence, or severity of the disease. Clinical measurements remain the single best method for assessing disease [38].

2.5. Advance in genetic testing

The last few decades have seen significant advancements in the field of genetic testing. In the past, kyrotype analysis—which counts the number of chromosomes and looks for duplications or deletions—was employed. Fluorescence in situ hybridization (FISH), which searches for particular smaller deletions like 22q11 deletion syndrome, came next. Comparative genomic hybridization and chromosomal microarray, which examine the entire genetic material at greater detail than karyotype and FISH, have been available more recently. The most recent technologies rely on next-generation sequencing, which examines each base pair of the DNA that codes for a protein. Whole exome sequencing (WES) or a gene panel for a particular disorder are the two testing options[39,40].

2.6. Host Genomics and Transcriptomics

Dental caries susceptibility varies among people, even when they exhibit the same lifestyle habits. The importance of the host-dependent milieu in selection of colonizing bacterial species has been validated, and the virulence of certain species could differ substantially among different ethnic individuals. The periodontium research has stepped forward by introducing the polymicrobial synergy and dysbiosis (PSD) model, which entails different gene combinations of dysbiotic microbiota and susceptible hosts for transition to periodontitis. However, there is no similar model for dental caries that encompasses possible host factors and their interactions with microbial communities in the maintenance of health or the shift to dental caries disease [41,42].

Host genomics and transcriptomics have been used to study the genetics of a complex trait such as dental caries since the mid-1900s. Candidate gene studies test specific hypotheses regarding association between specific genes and the disease, while genome-wide studies test the disease association with a large number of DNA variants throughout the genome. However, until 2017, nominated genes could not be confirmed due to population heterogeneity and statistical power issues[43].

Govil et al., 2018 conducted the first study applying the genome-wide multipoint linkage approach to make full use of familial inheritance to explore the genetic etiology of caries. They found significant associations between a number of SNPs and their resulting caries phenotypes, but there was uncertainty regarding the direct causality of these genes to dental caries. In a recent comprehensive collaborative work, forty-seven novel and conditionally-independent risk loci for dental caries were identified, showing that the heritability of dental caries is enriched for conserved genomic regions[44,45].

Transcriptome-wide association studies (TWAS) are a powerful approach that can detect novel disease loci or ascertain the susceptibility genes at known disease loci. Tong et al., 2020[46] conducted an integrative analysis of TWAS and mRNA expression profiling of dental caries to identify commonly associated genes and gene ontology terms.

Diagrammatic representation of the review process and design for the global evaluation of omics studies in dental caries research described in Figure 1 [46].

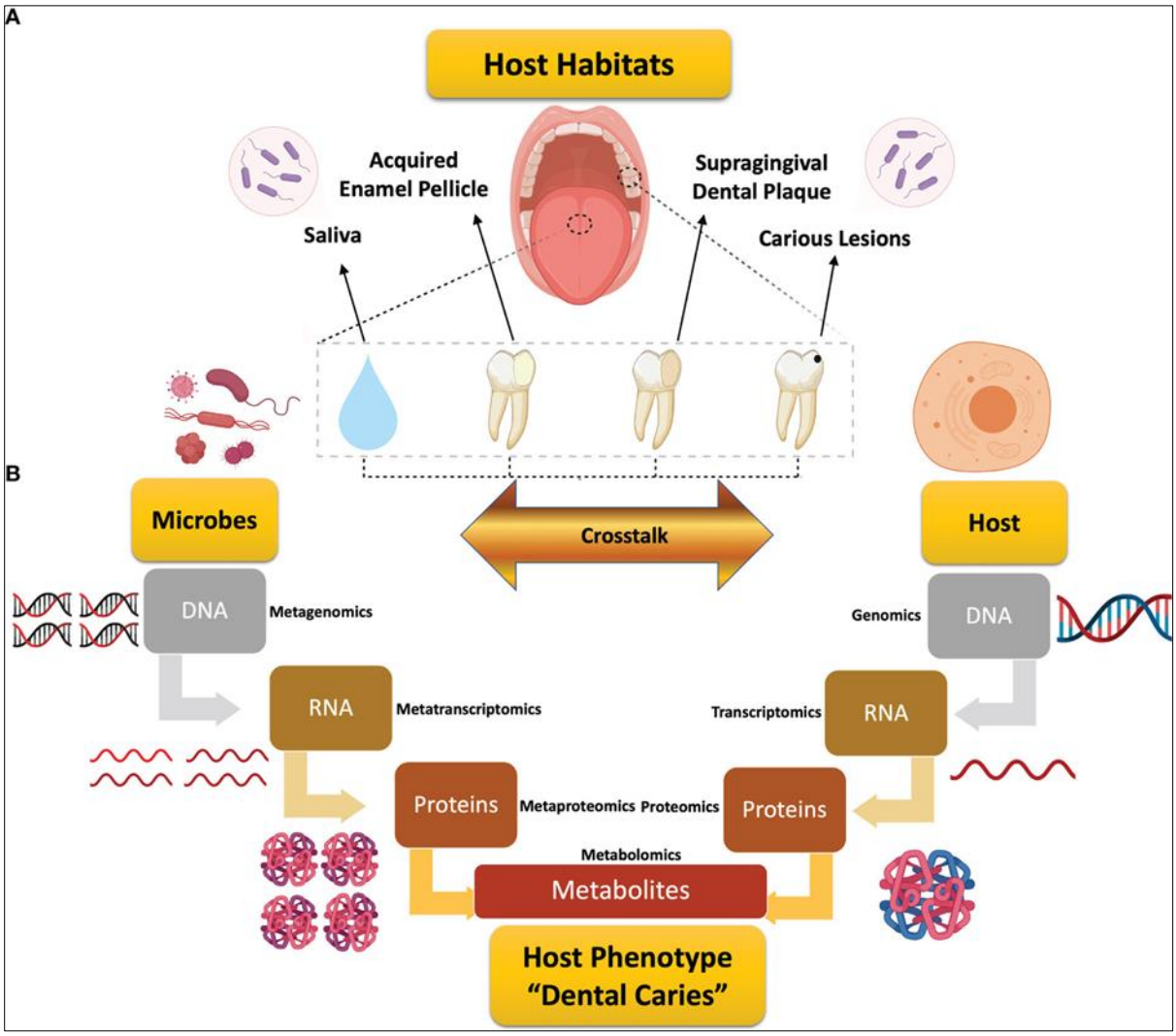

Figure 1 Global evaluation of omics studies in dental caries research.[46]

(A) An example of the review's scope for the host habitats under study in dental caries research. (B) An illustrative depiction of the information flow related to the microbiome and host along the central dogma of biology, starting from genomic data and ending with metabolic end products that may individually or in combination cause the expression of dental caries. From genomics to metabolomics, each step is linked to a corresponding systems biology tool, and an additional "meta" prefix that denotes "many" for the multispecies microbial communities is added. Microbial metabolism and microbial–host co-metabolism are encompassed by metabolomics, an analytical tool for metabolites.

3. Genetics and oral cancer

Oral cancer development can be influenced by inherited changes in genes. These changes can affect genes that normally promote cell growth (proto-oncogenes) or genes that suppress uncontrolled cell division (tumor suppressor genes). Examples of these changes include mutations in genes like GST (glutathione S-transferase) or CYP (cytochrome P450), or alterations in p53, p16, or APC genes. These genetic faults can lead to a loss of a healthy gene copy or an inability to repair DNA damage [43,46].

Researchers are exploring targeted therapies for oral cancer, particularly squamous cell carcinoma. These therapies focus on specific molecules involved in cancer development, such as genes, proteins, and signaling pathways. Promising targets include the epidermal growth factor receptor (EGFR), the vascular endothelial growth factor (VEGF), and pathways like MAPK/Erk and PI3K/Akt/mTOR. These pathways regulate cell growth, movement, and survival [47].

Current targeted therapies, when combined with traditional chemoradiotherapy, show improved effectiveness and reduced side effects. This dual approach has been successful in treating HPV-positive head and neck cancers. Another promising area of research involves inhibitors that target the PI3K/Akt/mTOR pathway, which is often activated in cancer cells and contributes to tumor progression and resistance to treatment [48].

Certain genetic disorders, like Werner's syndrome, Bloom syndrome, Fanconi's anemia, and ataxia-telangiectasia, can increase an individual's risk of developing cancer, including oral cancer.

Oral squamous cell carcinoma (OSCC) is a cancer associated with carcinogens, driven by both spontaneous and carcinogen-induced genetic and epigenetic events. Environmental agents such as tobacco, alcohol, and certain viral agents have been implicated in the development of OSC [42,47]. However, not everyone exposed to these agents develops OSCC. Inter-individual differences in susceptibility to carcinogenic exposures may result from differences in the interaction of genetic and environmental factors. Gender and racial differences in OSCC susceptibility have also been reported. Research to identify molecular determinants of OSCC now emphasizes a multidisciplinary strategy, including ecogenetic elements of susceptibility. Genetic damage is consistently found at all stages of carcinogenesis, leading to clonal expansion of unregulated cells [48.49]. Several forms of cancer, including breast, colon, and bladder, have been identified as requiring specific sequences of genetic damage for carcinogenesis. The importance of host genotype in OSCC is exemplified by emerging tumor progression models for oral squamous cell carcinoma. Classic epidemiological models have identified certain risk factors for OSCC.

3.1. Genectics and Craniofacial Malformations

Orofacial clefts (OFCs) are a group of disorders that affect approximately 1/700 live births worldwide, with varying incidences depending on factors such as geographic origin, racial and ethnic background, environmental exposure, and socioeconomic status. Although not a major cause of mortality in developed countries, OFCs are among the most common birth defects worldwide, causing considerable morbidity to affected children and substantial financial risk for families. Individuals may experience problems with feeding, speaking, hearing, and social integration, often requiring multidisciplinary and long-term treatment. Clinical manifestations of these defects are diverse, as they can occur as isolated, nonsyndromic anomalies or as part of the Mendelian syndromes [50].

Approximately 70% of CL/P cases are isolated, meaning they are nonsyndromic and not associated with any other recognizable anomalies. The remaining 30% of cases are classified as "syndromic," and present in association with other deficits or structural malformations. It is the role of the medical geneticist and genetic counselor to determine which cases are isolated and which are syndromic [51].

Understanding the genetic etiology of nonsyndromic CL/P has been traditionally difficult due to its complex multifactorial disorder displaying varying levels of penetrance, sex differences, and environmental overlays. Past genetic approaches to causative gene identification include linkage analyses and identification of chromosomal anomalies, while newer methods involve direct sequencing and genome-wide association studies (GWAS). Studies have shown strong evidence for the linkage of nonsyndromic CL/P to a region on chromosome 9q21, suggesting the significance of forkhead box protein E1 (FOXE1) as a susceptibility gene for nonsyndromic CL/P [35,45,52]
.
Syndromic Cleft Lip with or without Cleft Palate (CL/P) is a genetically distinct subgroup of orofacial clefting that occurs in 1/1,500 live births and is associated with at least 370 different malformation syndromes. Around 75% of these syndromes have a known genetic cause, including hundreds of Mendelian disorders resulting from a single gene defect. Common syndromes associated with CL/P include chromosomal abnormalities, microdeletion syndromes, and single gene disorders [53].

Cleft Palate Alone (CP) is embryonically a completely separate entity from CL/P and is associated with at least 370 different malformation syndromes. Approximately 50% of cases of CP are isolated while the other 50% are syndromic. Syndromic causes of CP include trisomies, microdeletion syndromes, single gene disorders, Pierre–Robin sequence, Schilbach–Rott syndrome, and Glass syndrome [54].

Several genes associated with the cleft palate phenotype have been identified, but the etiology of the majority of cases remain vague. Past studies of X-linked cleft palate localized the causative gene to be located on chromosome Xq21, pinpointing a variety of mutations in the TBX22 gene significant. Mouse studies show that targeted disruption of Tbx1 results in a wide range of developmental anomalies which encompass almost all of the common features of the DiGeorge/velocardiofacial syndromes [55].

Craniosynostosis is a relatively common birth defect that occurs in 1/1,000 births and can be presented in either a nonsyndromic (isolated) form or syndromic form. The most common craniosynostosis syndromes are due to mutations in the fibroblast growth factor receptor 2 (FGFR2) gene, which is involved in the signaling of immature cells to become bone cells during embryonic development. Eight known FGFR-related craniosynostosis include Crouzon syndrome,

Crouzon syndrome with acanthosis nigricans, Apert syndrome, Pfeiffer syndrome, Muenke syndrome, Jackson–Weiss syndrome, Beare–Stevenson syndrome, and FGFR2-related isolated coronal synostosis [56].

Muenke syndrome and FGFR2-related isolated coronal synostosis are two common craniosynostosis syndromes, with Muenke syndrome being the most common and requiring further molecular genetic testing. Muenke syndrome is autosomal dominant and caused by a point mutation in the FGFR3 gene, resulting in p.P250R (proline to arginine substitution at amino acid 250). Common characteristics include unilateral or bilateral coronal craniosynostosis, carpal and/or tarsal bone fusion, developmental delay, and sensorineural hearing loss. Associated anomalies may include mild-to-significant midface hypoplasia, ocular hypertelorism, and high-arched palate [57].

Microtia is a congenital anomaly resulting from a developmental malformation of the external ear. The prevalence of microtia varies among regions, with a particular increase in Hispanic, Asian, Native American, and Andean populations. Microtia can occur unilaterally or bilaterally, and can present in an isolated form or syndromic form. The most common associated malformations include facial cleft, facial asymmetry (hemifacial microsomia), renal abnormalities, cardiac defects, microphthalmia, polydactyly, and vertebral anomalies [58].

Developmental defects for some microtia-associated syndromes are more clearly understood as they reveal novel information on the molecular mechanisms involved in human craniofacial and ear development. Treacher Collins syndrome (TCS) is an autosomal dominant disorder of craniofacial development characterized by hypoplastic facial bones, microtia, micrognathia, and other deformities of the external and mid-ears, auditory pits, hearing loss, and cleft palate. Deletions on chromosome 22q11 cause DiGeorge syndrome and velocardiofacial syndrome, now known as 22q11 deletion syndrome. Clinical manifestations include craniofacial abnormalities, ear defects, hearing impairment, thymus and parathyroid gland hypoplasia, and cardiac malformations [59].

Nager syndrome is another syndrome commonly associated with microtia, presenting with micrognathia, external ear defects, external auditory canal stenosis, bilateral conductive hearing loss, cleft palate, downslanting palpebral fissures, high nasal bridge, hypoplastic or absent thumbs, and variable lower limb and toe defects. 18 different mutations in the SF3B4 gene, most of which are frameshift mutations, have been attributed to causing Nager syndrome. Other genes implicated with this syndrome include the homeobox genes PRX1 and PRX2, which have been linked to external, middle, and inner ear deficiencies [60].

3.2. Future consideration of Human Genetics & oral health

Genetics is a rapidly growing field in dental and medical education, enabling oral physicians to detect, prevent, and manage conditions affecting systemic and oral health. Diagnosis will involve clinical phenotype, differential diagnosis, and specific tests for genes and products. Both dentists and physicians must consider genetic variability and environmental interactions. Genetic counseling will address legal and psychosocial issues related to genetic screening, privacy, confidentiality, and communication of difficult issues. The interaction between human genetics and microbial genomics, proteomics, metabolomics, and pharmacogenomics will further enhance this field.

Oz, E., Kırzıoglu, Z [61] Investigated and compared the prevalence of dental caries and oral habits among children of multiple births and singletons, focusing on tooth brushing frequency and dental caries. Results showed that common environments like parenting style and social class may impact this practice. Children of multiple births are more likely to brush their teeth twice or more per day, possibly due to modeling by children of similar ages. Primary dentition caries have higher heritability than permanent dentition caries, with the highest incidence occurring between 1.5 and 4 years. Environmental factors, such as parental education and socioeconomic status, dietary habits, and access to dental care, could affect the progression and prevalence of dental caries. [62] Singletons had an increased caries rate compared to children of multiple births in the 2-5-year age group, although the children may have had low median m and f values since caries were in the initial stage and treatments for decayed teeth were minimal [60-63].

The identification of disease genes responsible for simple Mendelian traits has made significant progress, demonstrating the importance of understanding the genetic basis of disease and its pathogenesis at the molecular level. Although treatment of genetic disorders lags behind diagnostic capabilities, the emerging success in treating conditions like adenosine deaminase deficiency provides an example of the potential for developing effective diagnostic and therapeutic intervention strategies.[64] As the understanding of genetic mechanisms of growth and development becomes more sophisticated, it is now clear that most human traits with a significant heritable component are complex rather than simple. This is because more people are affected by these conditions, many are associated with significant morbidity and mortality, and many involve significant environmental factors. The identification of environmental factors associated with these diseases and their respective molecular targets will permit better intervention and

prevention strategies to be developed, particularly if it is possible to identify genetically susceptible individuals. Examples of complex etiologies with relevance to oral medicine include environmental modification, environmental triggers, interaction of a few loci, stochastic effects, heterogeneity, and differential mutations within a major locus [65].

The application of genetic medicine principles to the diagnosis and treatment of human diseases will fundamentally change healthcare delivery. As new information becomes available, it must be incorporated into healthcare paradigms that were not developed to handle such knowledge. This shift in focus from treatment to prevention raises important questions, such as the consequences of failure to inform individuals of risk and the individual's right to understand the genetic basis for disease.

Environmental agents interact directly and indirectly with genes and gene products, effectively modulating phenotypic expression of many simple and complex genetic traits. As our ability to identify and understand these interactions increases, we are presented with opportunities for intervention. Traditionally, complex conditions like cardiovascular diseases, diabetes, and some common forms of cancer have been difficult to study, and a complete understanding of the basic disease pathogenesis of these conditions is lacking.

Recent advances in research strategies and methodologies have revolutionized our ability to study and understand even these complex disease processes. The convergence of technological advances, informatics, and economic interests has galvanized government support for such endeavors. As society demands healthcare as a basic human right, advances in medical technologies are likely to continue at an unprecedented rate [65,67].

The role of oral care providers and education and training will also change, with the focus shifting from isolated care providers treating diseases and pathology after they have occurred to a more proactive approach[68,69]. Early assessment and treatment strategies will provide improved levels of care by targeting specific individual needs. The costs of such a health care system are difficult to gauge, but significant savings can be gained by treatment interventions that prevent significant disease pathology from developing [70].

4. Conclusion

The intricate dance between genes and oral health is slowly being unraveled. While genetics play a role in susceptibility to cavities, gum disease, and oral cancers, they are not the sole conductor in this orchestra. Environmental factors like diet, oral hygiene habits, and the oral microbiome play a significant counterpoint. The future of oral healthcare lies in this deeper understanding. By considering both genetic predispositions and environmental influences, we can move towards personalized preventive strategies and targeted treatments, ultimately leading to a future with healthier smiles for all

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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