Genetic modification on the disease of oral cavity

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Abstract:
Subtle changes to the genetic code can result in profoundly debilitating and diverse pathologies. The hereditary nature of human traits has been described since classical times. In the history of modern medicine, the first known genetic disorder, alkaptonuria, was described at the turn of the twentieth century, giving rise to the recognition of inborn errors of metabolism[1]. Diseases with their basis in mutations and alterations of the human genetic code represent a massive burden, and recognized genetic disorders affect more than 5% of live births and more than two-thirds of miscarriages[2].Beyond highly penetrant monogenic disorders and large-scale chromosomal alterations, the heritability of many common diseases has long suggested a genetic basis for more prevalent disorders such as cardiovascular disease [3].The prospect of passing genetic afflictions on to the next generation adds to the fear of these disorders. The first heritable alteration in a protein linked to disease was identified in sickle cell anemia in the late 1940s, with the discovery of altered shifts during electrophoresis, a change that

1.Introduction

Subsequently, once the DNA code for amino acids was deciphered, scientists recognized the potential for alterations in DNA to cause alterations in enzymes and thus disease. Prior to the advent of DNA sequencing, the cause of Down syndrome, identified in 1959 as the chromosomal abnormality trisomy 21, was the first human genetic alteration found to be associated with disease . Beginning in the 1960s, hereditary metabolic disorders such as phenylketonuria could be screened for biochemically without the need to know the causative gene's location or sequence[5]. The advent of Sanger sequencing and recombinant molecular biology in the 1970s and 1980s made the determination of DNA sequences widely accessible for the first time. The following decades, prior to the completion of the Human Genome Project in 2003, saw gene mapping consortia undergo herculean efforts to discover the causative genes in some of the most debilitating diseases, including the first mapped human genetic disorder, Huntington's disease, in 1983 . With the diminishing costs of exome and whole-genome sequencing over the past 2 decades, genetic diagnosis has become increasingly feasible, even for conditions that were not previously recognized as genetic diseases[6].

2.Gentic and human disorders

A genetic disorder is a disease caused in whole or in part by a change in the DNA sequence away from the normal sequence. Genetic disorders can be caused by a mutation in one gene (monogenic disorder), by mutations in multiple genes (multifactorial inheritance disorder), by a combination of gene mutations and environmental factors, or by damage to chromosomes (changes in the number or structure of entire chromosomes, the structures that carry genes)[6]. As we unlock the secrets of the human genome (the complete set of human genes), we are learning that nearly all diseases have a genetic component. Some diseases are caused by mutations that are inherited from the parents and are present in an individual at birth, like sickle cell disease. Other diseases are caused by acquired mutations in a gene or group of genes that occur during a person's life. Such mutations are not inherited from a parent, but occur either randomly or due to some environmental exposure (such as cigarette smoke). These include many cancers, as well as some forms of neurofibromatosis.[1]

2.1.Human Genomic Compartments

The genetic material in an adult human can be divided into compartments that differ in size, heritability, and diversity. The mitochondrial genome, the smallest (only 16.5 kb) but by far the most abundant, is inherited maternally and varies little among the human population. The traditional human genome contained in the nucleus is significantly larger and harbors mutations that cause the majority of traditional genetic diseases. The nuclear and mitochondrial genomes are determined at conception, although somatic mutations can drive mosaic disorders, cancer, and even aging.[7] More broadly, the adaptive immune receptor repertoire, which is a distinctive subset of the nuclear genome, and the microbial metagenome are determined only after conception, and their genetic complexity, at least as measured by the diversity of unique protein coding sequences, dwarfs that of the rest of the nuclear genome. The T and B cells of the adaptive immune system undergo somatic recombination, generating orders of magnitude more unique protein products than are possessed by the other genes of the nuclear genome, and together constitute the adaptive immune receptor repertoire. Finally, the nonhuman cells of the microbiome make up potentially the most dynamic and diverse genomic compartment of all, with a litany of different species, predominantly bacterial and viral, occupying structured niches across human skin, sexual organs, and

gastrointestinal and respiratory tracts. Both the adaptive immune receptor repertoire and the microbial metagenome vary significantly more among individuals, and increasing research aims to understand how genetic alterations in immune receptor repertoires and the microbiome contribute to disease pathology.[8]

2.2Gentics and dental caries

Dental caries is a common, multifactorial and chronic, global health problem that affects all age groups[9,10]Caries formation depends on various factors such as fermentable sugar, cariogenic microbial flora, host factors, time, diet, and other associated environmental factors[11,12]. Environmental factors such as low socioeconomic status, education level, medical health, lifestyle, diet, and accession to dental care can also affect the progression of dental caries. In addition, family size may be considered as an influencing factor for dental caries, as individuals having a big family are more likely to present high DMFT values[13,14].Dental caries occurs as a result of the association of environmental and genetic factors, including biological, social, behavioral, and psychological components[15].A cariogenic diet, oral hygiene habits, fluoride exposures, and the level of cariogenic bacteria can affect an individual's environmental risk factors. Components such as salivary flow rate, buffering capacity, localization of the tooth in the oral cavity, and surface properties of the teeth are also hosted factors that can affect caries formation[16]. The most associated microorganism with the dental caries process is mutans streptococci (MS). MS adheres to tooth surfaces and can produce acid. MS can also maintain metabolism in low pH conditions. Because of these properties, they contribute to the formation of caries[17]. In the process of dental caries, acids from bacterial metabolism diffusing into the enamel, and dentin dissolves the mineral. Thus, the formation of caries begins. Heredity from past to present is associated with dental caries in the literature. It has been determined that the caries risk may differ in people exposed to the same environmental factors. Thus, it was thought that genetic factors might also have an effect on the etiology of the caries.[11]. The role of genetic factors on caries risk was evaluated by examining the relationship between genetic studies and bacteria, studies in twins, gene polymorphisms related to salivary proteins, taste genes and nutritional preferences, and caries that have a huge effect in the etiology of dental caries[18]. In Genetic of bacteria and tooth genetic : The majority of studies investigating the correlation between dental caries and genetics, it is aimed to examine the gene variants of cariogenic bacteria, decode the genetic structures of cariogenic bacteria, and elucidate the metabolism of bacteria that cause dental caries. [15].The effect of S.mutansand its genotypes on dental caries was investigated and it was found that S.mutans is the primary cariogenic pathogen in the oral cavity and is caused by dental caries[19].The genes of amelogenin (AMELX), kallikrein 4 (KLK4), ameloblastin (AMBN), enamelin (ENAM), tuftelin (TUFT1) and tuftelin interacting protein (TFIP11), which are connected to enamel development and mineralization were reported as caries related genes. Among them, the combined effect of the TUFT1 gene with a high level of S. mutans was observed to increase susceptibility to dental caries. [16].

2.2.1.Risk factors of dental caries

A caries risk factor is defined as a factor/determinant, confirmed by temporal sequence and directly associated with an increased probability of caries. The identification of caries risk factors is important in epidemiology and clinical practice for the development of effective preventive strategies at both, the individual and collective levels[20].

-Risk factors,social\medical\Behavioral

• Hyposalivation (drug-, disease-, head/neck-radiation or/& age-induced)
• High intake (amount/frequency) of free sugars (drinks, snacks and meals)
• Low socioeconomic level, low health literacy, health access barriers
• Inability to comply, low motivation and engagement
• Special health care needs, physical disabilities
• Symptomatic-driven dental attendance

Risk Factors, Clinical-

• Recent caries experience and presence of active caries lesion(s)
• Pulpal/Roots/Sepsis caries-untreated consequences (PRS/prs)
• Poor oral hygiene with thick plaque accumulation
• Plaque stagnation areas (higher biofilm retention)
• Low salivary flow rate

Additional risk factors for children-

• Mother/caregiver with active caries lesions
• Bottle/non-spill cup/pacifier containing natural or added sugar
• Non-daily use of at least 1000 ppm fluoridated toothpaste
• Erupting molar teeth

Particular risk factors for elderly

• Exposed root surfaces (dentine)

3. Genetic and periodontitis

Periodontitis is a multifactorial inflammatory disease and both environmental and genetic factors play a major role in the progression of the disease with consequent tissue destruction around the dental roots, and alveolar bone is associated with systemic alterations such as diabetes.,[21], changes in the liver [22].cardiovascular diseases[23]and even osteoporosis [24].The high risk in the progression of periodontitis is directly associated with the biofilm found in the gingival sulcus, in which both amount and presence of specific species of bacteria represent risk factors [25].However, the genetic variability of host may influence individual susceptibility to disease development, so as to determine the clinical aspects and rate of periodontitis progression. The evidence

that periodontitis is a complex disease of multifactorial etiology has resulted in the development of focused researches in the identification of molecular markers capable of determining the risk of disease development[26]. Recently, investigations on factors of susceptibility to periodontitis have been gaining focus on genes of immunoregulatory molecules, such as cytokines, chemokines, membrane surface receptors, and antigen recognition proteins[25]. Cytokines such as interleukins (IL-1A, IL-1B, IL-6, and IL10, among others), surface receptors such as the Fcγ family (FCGRs), and cyclooxygenase- (COX-) 2 and matrix metalloproteinase (MMP) are considered key factors in the progression of periodontitis recruitment, differentiation and activation of B lymphocytes, inflammatory infiltrate, and stimulation of osteoclasts. Polymorphisms in these molecules have been suggested as factors that influence the risk of developing the disease . [27],although several studies using allelic and genotype frequency determination methods by Polymerase Chain Reaction (PCR) [28],or genomic association[29],have sought to clarify the relationship between polymorphisms in cytokines or other inflammatory mediators and periodontitis, if failures by the reduced sample number generate false-positive or false-negative data [25].

3.1. Dignosis of periodontitis

Traditionally, the diagnosis of the presence of periodontal diseases is made on the basis of evaluation of clinical signs and symptoms and may be supported by evidence from radiographs. Gingival changes including colour, contour, texture alterations and the presence of bleeding on probing from the gingival tissues allow the diagnosis of plaque induced gingival diseases. Non-plaque induced gingival diseases may necessitate other investigations such as histopathology, microbiology or serology to effect a diagnosis. Periodontitis is diagnosed by the presence of gingival changes as may be evidenced for gingivitis plus the presence of reduced resistance of the tissues to periodontal probing with a deeper gingival sulcus or "pocket" which reflects loss of periodontal attachment[30]. It is important to recognize that "pockets" may have a horizontal as well as a vertical dimension, thus the clinician in carrying out their probing for attachment loss must be careful to evaluate furcation involvements. The detection of attachment loss in furcations demands a sound knowledge of tooth and furcation anatomy, particularly the sites of the furcation openings on multi-rooted teeth. Tooth mobility and migration must also be assessed. It is, however, important to realize that mobility is not by itself diagnostic of periodontitis and may be the result of occlusal trauma as may be migration of teeth which may be segmental or single tooth migration. Mobility and migration solely related to periodontitis are usually late symptoms of the disease and are possibly of more importance in assessing prognosis and in treatment planning. Family history and factors which modify risk, such as cigarette smoking, stress, drugs or sex hormones, which affect the course of all types of periodontal disease need to be assessed and added to these primary descriptors to further describe the type of disease being diagnosed. Radiographs provide a secondary diagnostic tool and may demonstrate the presence of marginal bone loss, thus confirming the attachment loss. The role of radiographs in diagnosis will be addressed in another article in this supplement. [31]. It is generally agreed that the healthy gingival crevice can range from 1 mm to 3 mm. In health, the distance from the cemento-enamel junction to the alveolar bone crest is also variable and has a range of 1 mm to 3 mm. It must, however, be understood that attachment loss by itself does not constitute periodontitis which is an inflammatory lesion in the periodontal tissues and that health can exist in the presence of severe attachment loss and recession. Thus, a healthy periodontium can exist at different levels along the root as happens after successful treatment. The periodontal probe remains the primary diagnostic tool and is used to detect the presence of periodontal pockets as measured from the gingival margin to the base of the crevice and loss of attachment as measured from the cemento-enamel junction to the base of the crevice. Measurements recorded by the probe, however, are not in fact the actual pocket depth or attachment level but the distance from a fixed reference point to where the probe tip penetrates the tissues. This measurement will depend upon the probing pressure used, the tine size of the probe tip, angulation of the probe, the presence of subgingival deposits and, most importantly, the presence or absence of inflammation in the tissues. Thus, clinical attachment level and probing depth changes recorded during treatment may not reflect a true change in fibre attachment levels but merely changes in the depth of penetration of the probe into the tissues caused by change in the above factors[32]. Also Radiographic assessment: For patients with evidence of periodontitis, radiographic assessment is essential to provide information regarding the pattern and extent of alveolar bone loss. Guidance is provided by relevant authorities in different countries around the world, and for the purpose of this paper, the guidance issued by the Faculty of General Dental Practice (UK) will be described[33]. Regarding radiation dose, this appears to be less (when using modern panoramic machines) with a panoramic radiograph plus a small number of supplementary periapical radiographs (taken according to the clinical situation), compared to a full-mouth series of periapical radiographs . Furthermore, with modern panoramic machines, image quality is such that no additional periapical radiographs may be required. For these reasons, there is a trend to move away from exposing full mouth series of periapical images. Therefore, when using modern panoramic machines, it is recommended that a panoramic radiograph is sufficient to assess alveolar bone status, but this may be supplemented by selected periapical radiographs according to the specific clinical situation[34]. Whenever radiographs are obtained, a written report should be entered into the clinical notes. This should typically include factors such as:

teeth present (including unerupted teeth)/teeth missing.-

-bone loss, including pattern (e.g. horizontal, regular, irregular) as well as extent (usually expressed as a proportion or percentage of the root length).

presence of any specific vertical bone defects. -

- presence of calculus (supra- and subgingival).
- apical pathology.
- caries and enamel lucencies.

3.2 Risk factors of periodontitis

Main factor of periodontitis Associations between periodontitis and many other diseases and conditions have also been reported including respiratory disease; chronic kidney disease; rheumatoid arthritis; cognitive impairment; obesity; metabolic syndrome.

3.3. percentage of periodontitis

severe periodontal disease was the 11th most prevalent condition in the world.(GBD .2017) The prevalence of periodontal disease was reported to range from 20% to 50% around the world[35]. It is one of the major causes of tooth loss which can compromise mastication, esthetics, self-confidence, and quality of life [36]. Globally, periodontal diseases accounted for 3.5 million years lived with disability (YLD) in 2016 . (GBD .2017) During the period from 1990 to 2010, there was a 57.3% increase in the global burden of periodontal disease [37].In 2010, worldwide loss of productivity due to severe periodontitis was estimated to be US$54 billion per year [38].global prevalence of periodontal disease is expected to increase in coming years due to growth in the aging population and increased retention of natural teeth due to a significant reduction in tooth loss in the older population[39].Masticatory difficulties resulting from periodontal disease can interfere with the intake of food, thus negatively affecting nutrition and the general health of patients [40].In addition, periodontal disease is associated with other common systemic conditions such as diabetes, cardiovascular disease, adverse pregnancy outcomes, rheumatoid arthritis, and chronic obstructive pulmonary disease [41]. The metastatic spread of microorganisms and their products from dental plaque and inflammatory mediators from periodontal tissues to other organs of the body is believed to account for this periodontal and systemic disease connection [42]. Different segments of the population are disproportionally affected with periodontal disease[43].Evidence has suggested an inverse relationship between income and periodontal disease [18,44]It was reported that low-income individuals had 1.8 times increased odds of severe periodontal disease than high-income individuals[43]. Periodontal disease inequalities exist among different age groups, and the severity of the disease increases with advancing age. In an epidemiological study, it was found that the highest prevalence of chronic periodontist was found in the elderly population (82%), followed by adults (73%) and adolescents (59%) [19,45].It is known that periodontal disease can be prevented; however, patients with periodontal disease usually seek oral care when the disease reaches an advanced stage because its early stages are usually asymptomatic . Therefore, early diagnosis and treatment are crucial for the maintenance of periodontal health. The analysis of global data about the prevalence of periodontal disease is useful for policy development and the allocation of financial and human resources for preventive measures and the provision of treatment. However, the prevalence of periodontal disease in different age groups and in low-income, middle-income, and high-income countries is not fully understood. Therefore, this study aimed to compare global data of periodontal disease among population of adolescents, adults, and older persons. The study also evaluated the prevalence of periodontal disease in low through high-income countries[38].

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