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Genetic and Psychology Factors Involved in the Cariogenic Process: A Literature Review

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Abstract

Dental caries is a dynamic and multifactorial chronic disease, which has a prevalence of up to 80% in South American countries, so it is the focus of multiple investigations based on elucidating the genetic model of this pathology which would contribute to a personalized treatment and diagnosis of the same, this model proposes four pillars around the susceptibility to this pathology, the first of them is based on the genes involved in the development of enamel finding AMEL, ENAM, AMBN, MMP TUFT1 and KLK4, passing through the genes associated with taste whose polymorphisms are TAS1R2 and TAS1R3, in this same line are the genes associated with signaling pathways RPS6KA2, PTK2B, TLR2 and BTF3 and finally the genes of the Human Leukocyte Antigen (HLA), although there are several polymorphisms associated with susceptibility, some need to present a specific isoform, a mutation or a cofactor to trigger an imbalance in the oral environment that leads to the genesis of caries.

Keywords. Genetic polymorphism, genes, Dental Caries Susceptibility

Introduction

Genetics is the science that analyzes the molecular composition of DNA, its replication and gene function. (1) In the scientific field, DNA has been described as a fundamental molecule that is capable of encoding the genetic information of all cells and the variety of traits reflected by molecular markers, gene polymorphisms that are located in the coding region of the genome, that is, in regions capable of coding for a protein, which may or may not have effects on the phenotype, On the other hand there are genetic polymorphisms which are located in non-coding regions ie that are not qualified for the coding of gene products, despite this they can fulfill regulatory and structural functions and finally we find the Single-Nucleotide Polymorphism (SNP), which influence a single nucleotide of the genome and are associated with diseases such as diabetes (2).

Certain structures such as enamel and dentin may have structural changes at the cellular level in certain individuals who may be predisposed to pathologies, polymorphisms allow detecting variability in the perception and attraction to foods rich in sugar, this added to the time of exposure to acids produced by microorganisms such as *Streptococcus mutans* They result in progressive deterioration of the dental organs.(3)

Dental caries defined as the dynamic and chronic multifactorial condition that occurs due to mineral imbalance in the oral environment, the importance of its study lies in the high incidence that occurs nationwide, reaching about

60% in the population and in South America reaches figures above 80% (4), is a disease multifactorial, by which in the genetic field reveals the positive mutuality between the susceptibility to present it and the genetic factors involved by which the genes involved in the morphological development of enamel, genes of the perception of flavors, genes of the signaling pathway and genes of the Human Leukocyte Antigen (HLA) are studied.
Therefore, this literature review seeks to recognize the main polymorphisms that will increase the susceptibility to caries, as well as identify their mechanism of action and frequency.

Methods

In this research, a descriptive and comparative study has been conducted on scientific reports with high impact factor in the area of dentistry and genetic genomics. First, we searched the specialized literature in databases: Google Scholar, Scopus, Elsevier, PubMed, Zlibrary, Springer, Mediline, using as input the keywords: Polymorphism, genes, susceptibility, caries, proteins. A time range of a decade 2010 to 2020 was used and 116 articles were selected, then through the inclusion and exclusion method, duplicate articles and original articles that did not contain studies in relation to polymorphisms related to the cariogenic section were excluded, as well as opinion articles and editorials, original and review articles with a high-level scientific report were included, which in their highest percentage, contained information on the proposed indicators, so 47 articles were selected, analyzed and discussed in this review.
The analysis began with the polymorphisms involved in the development of enamel and its mechanisms of action, after which we identified the polymorphisms in relation to the perception of flavors, signaling pathway and human leukocyte antigen

Results

Genes coding for proteins involved in enamel

There is a diversity of genes involved in the process of enamel formation, many of them are essential for enamel to have its particular characteristics, when there are alterations mutations and translocations at the level of these genes the information they provide at the cellular level results in abnormal pathological processes or structurally deficient (6). It has been shown that disorders at the level of these proteins do not always lead to amelogenesis imperfecta since they can alter the normal structure of the enamel giving greater susceptibility to present carious processes, genes such as AMEL, ENAM, AMBN, MMP TUFT1, KLK4 are recurrent polymorphisms associated with enamel defects (7). The genes associated with these polymorphisms are detailed below.

AMEL

The genes of Amelogenin X and Y (AMLEX and AMLEY respectively) are genes that are located on the short arm of chromosome X and Y, this is responsible for encoding the hydrophobic protein amelogenin, which is essential for the formation of enamel. (8). Specifically, they intervene in the agglutination of hydroxyapatite crystals to build the structural rod that represents about 90% of the enamel constitution. (9)
The gene that presents the DNA sequence with the information of Amelogenin may present alterations or mutations that result in inherent characteristics in the individual that presents it, leading to susceptibility to caries (10). We describe the mutations and alterations of this gene that has relevance in relation to the susceptibility of the cariogenic process (11).
The gene that controls the protein Amelogenin presents several mutations, directly linked to susceptibility to caries, the AMLEX gene located on the X chromosome on the short arm in region 22 in band 3 (Xp 22.3), in the same way this gene is coupled to the X chromosome in the short arm region 22 band 1 (Xp 22.1). The mutation of this gene causes the protein amelogenin not to fulfill its function properly or in turn to completely change the function, when there is a permutation within the sequence of nucleic acids present in the DNA, the gene mutates when a single nucleotide is altered or by default when a sequence of three nucleotides is alteredos (codons) (12). DNA has a chain of nucleotides that provide precise information to the cell so that it can produce Amelogenin in the enamel composition phase.(13)
The amelogenin gene is characterized by being a codominant gene this because it has a dominant genotype, which is why the AMELEX polymorphism having this characteristic can increase susceptibility in an individual if their parents have an identical polymorphism or a version that differs minimally from it (14) (11)(15).

This is the case of polymorphisms of AMELX both hCV2190967 and rs178784860 which have an MFA of 0.06 and 0.08 respectively can be categorized as an unusual genomic variant in people carrying the gene has been described a greater susceptibility to caries when presenting a T and C allele.(16) (17) (18)
Within the polymorphisms of the gene of the protein Ameloblastina there is a variant that takes special relevance in our research, this gene of dominant, codominant or overdominant character, have a direct impact on the predisposition of the individual to present caries. The rs946252 gene has a frequency of AFM 0.31 (usual) experimental studies in specific populations have yielded results that show that this gene has a predisposition for gender, acting in a protective way in the male gender (T allele), and in the female gender presents direct susceptibility to caries regardless of the variation of alleles (19).

ENAM

ENAM gene coding Enamelin, a protein that helps the formation of enamel specifically in amelogenesis, the physical properties of the same depend on the expression of this protein in conjunction with AMLEX and AMBN, several authors claim that enamelin is an adjuvant in the process of elongation of hydroxyapatite crystals in developing enamel, Located on the long arm of chromosome 4 in region 11 and 21(21)(22)
ENAM variations can be given by several mutations at the level of the nucleotide sequence of DNA which lie in base changes either by transition, transversion, deletion or insertion and transposition (19) (23).
When the genotype is recessive genotype GG mutation at the level of ENAM can be presented as a protective factor against ECC (Early Childhood caries), which shows a great variety to the susceptibility to caries in children who have similar predisposing factors in relation to this pathology, the specific polymorphism of this gene is rs1264848, AFM = 0.11 (common). (24).
In relation to the mutations that predispose susceptibility to caries we find the ENAM rs2609428 (uncommon) which alone is associated with dental caries and on the other hand we find rs767128, rs3796704 which are haplotypes, which are considered common (MFA = 0.12) (25).
ENAM rs12640848, rs3790506 which present a mutation by transversion in a single nucleotide, when there is a haplo insufficiency, that is, when the specific copy of the gene is inactivated or completely eliminated, this mutant gene does not have the ability to produce the amount of gene product that is needed to maintain optimal functioning, at the level of this protein the overall result is a significant reduction in the amount of enamelin available during the Amelogenesis process resulting in dental hypoplasia (19)(26)

AMBN

Gene encoding the phosphorylated glycoprotein ameloblastine responsible for the cohesion of hydroxyapatite crystals (27) which is secreted by the ameloblasts of the enamel matrix, its main function is to adhere the ameloblasts to the basement membrane; When this protein is altered, the segregation of ameloblasts is caused, compromising their polarity and their function of secreting amelogenin. (28)

The mutations suffered by this gene either by deletion, duplications or transition, it is claimed that they have a direct influence on cariogenic processes, the most representative polymorphisms of AMBN are rs4694075 and rs34538475 which present a transition alteration (C to T) with a frequency MFA = 0.48 and MFA = 0.17 respectively cataloged common. (26)

MMP

Metalloproteinase 20 (MMP-20) is a gene located on the long arm of chromosome 11 region 22 band 3 (11q22.3) encoding the extracellular matrix protein enamelisina which is secreted by both ameloblasts and odontoblast, this participates in the development of enamel eliminating excess organic components and facilitating mineralization in both enamel and dentin. (30)(28)

MMP-20 has a direct relationship with the other proteins that act in the formation of enamel especially with amelogenin since it processes the N-terminal of this protein and act at the most water-soluble point of this formation which is known as TRAP (Thiamine Rich in Amelogenin Peptide Rich in Tyrosine); Mutations at the level of this gene cause that enamelisina does not comply with the elimination of waste generated by proteins involved in the process of enamel formation, have identified at least 7 mutations in This gene, which gives

abnormal characteristics to the enamel presenting rough, discolored, prone to ruptures and caries, is considered uncommon as it is a recessive genotype (31) (32) (33)

The polymorphism highlighted in relation to the MMP20 gene is rs1784418 which increases The risk of caries by presenting a transition in the transcription process in the nucleotide sequence, thus causing the hypomaturation of the enamel, that is, a less intense mineral surface that presents areas of immature enamel (34).

KLK4

Kallikrein 4 is a serine protease, which releases serines through odontoblasts and ameloblasts, participates in the formation of enamel by degrading the protein amelogenin before completing the hardening of the enamel, located on chromosome 19, its mutations rs198968 prevents the appearance of early childhood caries, rs2235091 increases resistance to caries when it presents transition. (28)

TUFT1

The TUFT1 gene participates in the structural processes of the enamel and as well as in its development, this gene encodes the protein Tuftelina being indispensable for calcification, specifically in the phase of nucleation and growth of crystals (35). It is located on chromosome 1 on the long arm in region 21 (1q21) and its expression occurs in very early stages of odontogenesis where ectodermal/mesenchymal interactions culminate in the production of ameloblasts and odontoblasts (43).

The mutation rs2337359 is linked to caries in adults, rs3790506 presenting a codominant genotype GG provides caries in early childhood. When there is a transversion in the rs2337359 and rs3790506 polymorphisms, the susceptibility to caries increases, presenting an MFA index of 0.22 and 0.14 (common). (24)

There is a polymorphism of the TUFT1 gene that is the product of a transposition of the original nucleotide chain, when presenting these two variants (CTTCTCAAGGT / CTGTAGGAAGA) added to the accumulation of plaque, drive the *Streptococcus mutans* and predispose to the appearance of carious lesions (29).

Polymorphisms related to taste perception

A mutation can enhance that certain individuals have a diet rich in sugars and carbohydrates, we refer to the polymorphisms TAS1R2, TAS1R3 that influences the reception of sweet flavors with high sucrose content (36), its mechanism of action lies in the codominance, in the subjects that present these polymorphisms the Stephan curve is prolonged the time for the saliva to recover its normal pH after having descended to a critical pH(37)

Related polymorphisms have been reported in the development and form of perception of the taste buds, since in several individuals little sensitivity to the perception of sweet flavors has been observed, so the intake increases and therefore the individual requires greater amounts of sucrose to reach a point of satisfaction. (38).
Among the polymorphisms associated with taste perception we find TAS1R2 rs35874116, rs3935570, rs4920566, rs9701796, and TAS1R3 rs307355 (38)(39)

Signaling pathway genes

The MAPK signaling pathway has a link with dental caries and RPS6KA2 and PTK2B polymorphisms have been identified that participate in dentin mineralization, since both genes encode respectively the family of serine / threonine kinases RSK and protein tyrosine kinase, protein kinase by means of phosphorylation will activate or inhibit the function of threonine proteins, tyrosine and serine, which in vitro participate in dentin mineralization. (40) (41). The TLR2 gene presents the genetic information for the construction of the family of proteins that are part of the innate immune system: The Toll-like receptors themselves that are highly specialized in signal translation, recognizing pathogen-associated molecular patterns (PAMPs), once these patterns are identified, odontoblasts are able to produce nitric oxide agent that acts as a bactericide, TLR2 is also capable of producing mast cell monocytes, B and T lymphocytes, macrophages and myeloid dendritic cells, the rs11099896 polymorphism inhibits immune activity since it is not able to recognize gram positive and gram negative bacteria

causing a deficient reception of the stimuli that TLR2 requires for the immune and odontoblastic response resulting in an acceleration in the cardiogenic process blocking the immune response to the aggressors (42) (43).

The BTF3 gene is a biomarker expressed in saliva that is associated with caries experience, when it presents a specific isoform, in the presence of a nuclear factor kB1 this gene acts with an antimicrobial effect resulting in a protective gene against the cariogenic process. (45)

Human leukocyte antigen genes

The Human Leukocyte Antigen (HLA) represents a set of genes related to the Major Histocompatibility Complex (MHC) that encode proteins on the surface of the cell that have an important role in immunoresponse, there are two classes of MHC, class I depends on the HLA-A, HLA-B and HLA-C genes and class II depends on LA-DPA1, HLA-DPB1, HLA-DQA1, HLA-DQB1, HLA-DRA and HLA-DRB1.3

The genes that help the immune activity against bacteria are modified by the molecule HLA II, alterations in these genes have been involved in bacterial growth activity especially in *Streptococcus Mutans,* main enamel colonizer and *Lactobacilli Acidophilus and Lactobacilli Casei* Main colonizers (41)(43). HLA II and class I and II antigens eradicates the action of *Streptococcus Mutans* on the surface of the enamel, several reports agree that the HLA DR4 gene, by altering the presentation of antigen I and II increases susceptibility to caries, finding a constant marker in adolescents with present and past history with caires (41) (15)(45).

Discussion

Caries has reached an incidence of up to 60% in the population, its etiology is variable so the genetic section has great relevance since at the beginning of the XXI century it acquired notoriety with studies prepared by Deeley (26). Over the years, polymorphisms with direct susceptibility have been discarded and discovered. Ken Ouryouji et al (2008) stated that the AMELX rs6639060 polymorphism presented a susceptibility factor to caries, but in 2016 Yildiz et al. described that this polymorphism had a null appearance in caries (16)(11)

In relation to AMELX and its polymorphisms rs946252 and rs17878486 have been described its direct relationship with susceptibility to caries when they undergo a transversion that prevents the coding of the protein amelogenin, in contrast, Roohollah Sharifi in his meta-analysis states that these two polymorphisms do not influence the susceptibility to present carious lesions this due to the ethnic factor (11)

Several investigations converge on the same premise: AMELX (rs946252, rs178784860), ENAM (rs3790506, rs12640848), AMBN (rs4694075, rs34538475), MMP, TUFT1 (rs4970957, rs3796704) and KLK4 (rs2235091) all these when presenting a mutation increase the susceptibility to caries, on the other hand there are protective factors that decrease the susceptibility of caries to the carrier regardless of the habits they possess referring to two protective polymorphisms ENAM rs1264848 KLK4 rs198968 TUFT1 rs3790506 (19)(45)(26)

In the section of polymorphisms associated with taste perception, Wendell S, describes the TAS2R38 gene that encodes a protein of taste sensation and correlates it with susceptibility to caries, simultaneously in the studies of Wendell S, it is described that this gene and its polymorphisms have a direct influence on the creation of eating habits in adulthood, however, Melania Melis in 2019 argues that this gene presents an association with the perception of bitter tastes and Smith. J.L adds the relationship of the same with the consumption of vegetables. So it is inferred that this gene does not have a close link to caries susceptibility unlike TAS1R2 and TAS1R3 that directly influence since they have a link with the perception of sweet flavors and their frequency of consumption, a factor that conditions the body mass index.(39)(47)

Conclusions

- AMELX is the most important gene, since it encodes the protein amelogenin itself that influences the prismatic formation of hydroxyapatite crystals and constitutes 90% of the proteins of the extracellular matrix, establishing the mineral characteristic of enamel, the most outstanding polymorphisms is rs946252 because it presents greater predilection to the female gender in view of showing greater susceptibility to caries difference from the male gender where it acts in a protectress.

- ENAM, gene that encodes the protein enamelina the same that is basic for the structural formation of the tooth, in its absence is a cofactor in the process of elongation of crystals in the development of enamel, presenting a genotype GG acts as a protective factor in caires of early childhood, within the polymorphisms that give susceptibility to caries rs2609428 being the most outstanding in clinical studies.
- The gene encoding the phosphorylated glycoprotein ameloblastina AMBN is responsible for the cohesion of hydroxyapatite crystals, before mutations in this gene clinically enamel is observed Hypoplastic.
- Metalloproteinase 20 is involved in the expression of enamelisin protein that is responsible for eliminating excess organic components facilitate mineralization in both enamel and dentin, the most prominent polymorphism around MMP-20 is rs1784418 which causes enamel hypomaturation.
- The protease responsible for degrading the protein amelogenin before the end of the hardening of the enamel is Kallikrein 4 in which two polymorphisms have been reported where they intervene in a protective way against caries in infants
- The protein tuftelina which is considered essential for calcification, presents two relevant polymorphisms, since rs2337359 promotes susceptibility to caries in adults, the mutation rs3790506 shares a characteristic with the aforementioned polymorphism that provides susceptibility to caries in early childhood.
- It is evident that TAS1R2, TAS1R3 are genes that intervene in the perception of sweet flavors specifically, this premise is evidenced in that some individuals need greater amounts of sucrose to feel cloyed, this added to the consumption of cariogenic foods between meals, makes Stephan's curve remain at an acid pH of 5.5 leading to the demineralization of enamel.
- TLR2 and BTF3 signaling pathway genes influence immune response to cariogenic microorganisms, BTF3 brings promise of personalized treatments for caries
- The Human Leukocyte Antigen gene, HLA DR4 is a constant marker that manifests in early childhood caries.

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