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EXPERIMENTAL STUDY

Genetic factors affecting susceptibility to dental caries

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ABSTRACT

Dental caries remains the most prevalent chronic, oral biofilm-associated disease affecting majority of the globe's population in all age categories. Despite enormous and revolutionary progress in omics technologies, it´s aetiology is not fully understood. The interest of current research is primarily focused on the identification and understanding of the crosstalk between main players such as host cell genome, oral microbiome´s genome, factors of immune response, saliva content and nutrition. For accurate, multi-omix analyses, it is essential to know which patient´s genes enter into crucial interactions. Identifying genes and understanding the mechanism of their action is the key for deeper understanding of their involvement in the pathogenesis of this disease. Serious alterations of these genes should be consequently used as markers to determine the extent of genetic predisposition to dental caries and identify susceptible patients. That should significantly improve the prevention, diagnostic and therapy of the disease with an individual approach and provide more efficient and effective implementation of newer preventive measures and novel therapeutic approaches in the management of the disease. This review focuses on contemporary evidence on genetics factors affecting dental caries and to provide an up-to-date comprehensive description and classification of the genes and their alterations influencing the disease. It also aims to delineate and discuss evidence gaps and potential novel applications of genetics in the context of recent advances *(Tab. 2, Ref. 113)*. Text in PDF www.elis.sk
KEY WORDS: dental caries, candidate gene, genetic variation, multifactorial disease.

Introduction

Dental caries is a complex, chronic, multifactorial disease and one of the most prevalent diseases in industrialized as well as in developing countries (1). According to WHO data from March 2020, untreated caries of permanent teeth is the most common disease, and it is estimated that 2.3 billion people are affected by caries of permanent teeth and more than 530 million children are affected by caries of primary teeth (2, 3). According to the ADA (4) tooth decay is one of the most common diseases, affecting 97% of the population worldwide. In developed countries, it is 60-90% of children and almost 100% of adults (5).

A study from 2015 (Global burden of untreated caries) covers the period of 1990–2010 and says that during 20 years, the incidence of dental caries in primary dentition has not changed and is still the highest in the 6th year of life, regardless of gender. The same conclusion was also found in the permanent dentition, where the peak is in the 25th year, equally without gender difference. Furthermore, it was found that dental caries has one of the highest incidence in permanent dentition in Central Europe (6).

However, the overall incidence of dental caries in Europe has decreased during the last decades, mainly in children and adolescents, while the situation in adults and seniors has hardly changed in recent years. We date the decline in prevalence from 1960, with the most significant decline in the Scandinavian countries, Switzerland, Great Britain, Ireland and the Netherlands (7).

According to the WHO Global InfoBase (a global oral health database, providing results from national and community programs aimed at promoting and preventing disease), the American and European regions are much more affected by dental caries than the world average. The smallest incidence of tooth decay is in the African region. The countries such as Serbia, Montenegro, Ukraine and Slovakia are countries with a very high, globally above-average incidence of dental caries. Conversely, countries with a very low incidence are Great Britain, Germany and Denmark (8).

During the past few decades, the population has polarized as to oral health level, mainly in young generation. A part of population has bad and neglected oral condition and no access to professional care caused by many different risk factors. Another increasing part of population has low caries experience and good professional and

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home care since childhood. It could be connected also with higher socio-economic level and education of parents (9).

Based on the preliminary analysis, the lifetime costs of dental caries represent a significant burden on individuals and health systems. The lowest socioeconomic groups in each country face the greatest health and economic burden from the disease. By targeting preventative interventions to reduce the incidence of dental caries, there is considerable potential for individual countries to improve oral health across their population (10).

Furthermore, the health policies adopted by the National Health Systems in most countries seem inadequate to reduce the inequalities in oral health between socially vulnerable and non-vulnerable people. Therefore, it should be considered to stimulate health policy makers to adopt measures, both legislative and economic, which are more protective of socially vulnerable subjects. In fact, the loss of oral health inevitably creates a negative impact on the overall health of the vulnerable worldwide, with significant financial consequences for National Health Systems and for the global general population (11).

Even the aetiology of dental caries is still not fully understood, it is mainly influenced by environmental factors such as diet, dental plaque, oral hygiene habits and others (12). In healthy people with proper nutrition and sufficient oral hygiene, the microbiota coexists in symbiosis with the host, maintaining a balance that determines oral health as well as the body as a whole (13). However, these factors cannot always explain its increased occurrence even in groups where these factors are eliminated, or their influence is relatively low. Based on the results of numerous studies and research, it is now well known that genetics play an important role in the aetiology of dental caries too (14–20). Identifying genes with strong association to dental caries and illuminating their function is the key to understand their impact in convoluted interactions of all relevant factors. Genetic variations could act as markers to determine the individual susceptibility to this disease and that would help to better understand the contribution of genes in caries etiopathogenesis and significantly improve the prevention and therapy of the disease.

In this review the authors focus on the description and classification of genes and their forms directly or indirectly involved in the development of dental caries.

Dominant factors affecting development of dental caries

As it was already mentioned, dental caries is a multifactorial disease, influenced by interaction between genetic background, behavioural, environmental and socio-economic factors (20–25). Dominant environmental factors influencing development of dental caries can change over time and include cariogenic bacteria, quantity and quality of saliva, dental hygiene, fluoridation and food composition.

Hereditary predisposition depends on many so-called genes of small effect that have an additive effect. Involved alleles create mutual combinations and under the strong influence of environmental factors participate in the formation of the given trait (26, 27).

Last decades were rich for studies focusing on detection and better understanding of incriminated genes.

One of the first and most famous studies was provided by Gustafsson et al (1954), who observed the connection between the type of diet and the occurrence of dental caries. They found that 20% of the participants did not develop any carious lesions during the study period, despite a diet rich in sugars, while the remaining 80% experienced a dynamic increase in their incidence during the same time period (28).

Shaffer et al (2013) on the basis of research, state that people with similar habits such as frequency of tooth brushing, dental hygiene, fluoridation and eating habits have different rates of dental caries incidence and that caries occurs at an increased frequency in certain groups despite increased fluoridation (29).

The fact that susceptibility to caries is the result of the influence of genotype and environment, or both simultaneously, was repeatedly described (1, 30, 31).

Very interesting and valuable results are often obtained thanks to twin studies, which have been used for over 50 years and are still popular. These studies looked at caries incidence in monozygotic and dizygotic twins, and investigated the genetic predisposition to caries (32–39). They confirmed that the genetic background plays an important role in the aetiology of dental caries, as a higher similarity between monozygotic than dizygotic twins was demonstrated (1).

One of the other large studies conducted by Khan et al (2020) focused on investigating the incidence of dental caries in the household based on the DMFT/deft index (the number of broken/fallen/filled teeth or tooth surfaces due to tooth decay) (40). 2000 couples participated in the study, of which 400 (20%) were consanguineous couples and 1600 (80%) non-consanguineous couples. The study then also followed their children, who were aged 6–9. The results of this study proved a significantly higher association of „deft“ scores in the group of children from consanguineous marriages. The conclusion of the study was the finding that tooth decay has a multifactorial etiology, in which both environmental and genetic factors play a role and influence increased susceptibility to tooth decay.

Genes involved in the etiology of dental caries

Many of standardized methods such as Candidate Gene Studies, Genome-wide Association Studies, Genome-wide Linkage Studies and Analysis of Quantitative Trait Loci, that brought clarification in genetic component, allowed to identify genes that can contribute to the risk or resistance to the development of dental caries. Based on their effect, these genes can be classified into four groups:

- *Genes involved in the tooth formation – development of hard dental tissue*
- *Genes influencing the immune response to cariogeneic bacteria*
- *Genes influencing quantity and quality of saliva composition*
- *Genes determining taste preferences*

The list of all candidate genes can be found in Table 1.

Tab. 1. The list of all candidate genes.

	GENE	ENCODED PROTEINS AND FUNCTION	ROLE IN CARIES PATHOGENESIS
Genes involved in tooth development	***AMELX / AMELY***	**Amelogenin** Formation and regulation of enamel	Formation of defective and less resistant enamel, in case of mutation – amelogenesis imperfecta
	ENAM	**Enamelin** Formation and regulation of enamel	Formation of defective and less resistant enamel, in case of mutation – amelogenesis imperfecta
	AMBN	**Ameloblastin** Formation and regulation of enamel	Formation of defective and less resistant enamel, in case of mutation – amelogenesis imperfecta
	TUFT1	**Tuftelin** Formation and mineralization of enamel	Formation of defective and less resistant enamel; association with higher caries incidence at higher level of S.mutans
	KLK4	**Kallikrein-4** Formation and maturation of enamel	Protective character – associated with lower caries risk
	MMP20	**Matrix metalloproteinase-20** Degradation and remodeling of extracellular matrix of enamel and dentin	Supporting progression
	MMP13	**Matrix metalloproteinase-13** Degradation of extracellular matrix and bone remodelling	Protective character – associated with lower caries risk
	MMP16	**Matrix metalloproteinase-16 transmembrane protein** Tooth development – regulation of ameloblast maturation and enamel formation	Formation of defective enamel and malfunction of ameloblasts
	PKD2	**Polycystin-2** Transmembrane protein, intercellular matrix interaction	Its deficiency leads to craniofacial and dental defects (fractures of molar roots, changes in the shape of incisors, loss of alveolar bone), which predispose the dentition to higher susceptibility to the development of caries
	ABCG2	**ATP-binding cassette subfamily G member 2, membrane transporter** Transport of molecules from extra- to intracellular space in different tissues	Expressed in dental pulp, potential protective role by blocking the absorption of various substances, its role in the pathogenesis of caries is not clarified
	SCPP family	**Secretory calcium-binding phosphoprotein family** Mineralization of enamel and dentin	Increased tissue mineralization and higher resistance of hard dental tissues – a protective factor.
	NEDD9	**Enhancer of filamentation 1** Development and migration of neural crest cells	Formation of defective enamel and dentin
Genes related to the immune response	***PRH1, PRH2***	**Salivary acidic proline-rich phosphoprotein 1/2** Maintaining tooth integrity, inhibiting bacterial adhesion to the tooth surface, inhibiting pH drop, inhibiting HSV1 replication	Association with a higher incidence of dental caries with the expression of the Db allele – support for biofilm growth
	DRB1	**HLA antigen** Recognition of pathogens and initiation of the immune response	The presence of HLA DR4 and DR3 increases the risk of caries; they are also correlated with a high concentration of S. mutans.
	DQB1	**HLA antigen** Recognition of pathogens and initiation of the immune response	Allele HLA DQB1 protective marker – associated with a lower incidence of dental caries.
	LTF	**Lactoferrin** Multifunctional immunomodulating effect – bacteriostatic – binds iron; neutralization of surface tension of bacteria; blocking bacterial adhesion, affecting membrane permeability	Protective factor – associated with lower incidence of caries – high lactoferrin activity but has variations that are associated with lower lactoferrin activity – higher susceptibility to the development of dental caries.
	DEFB1	**Defensin beta 1** Antimicrobial and cytotoxic peptide – chemotactic activity; stimulation of cytokine production in epithelial cells; mast cell degranulation; cell lysis by increasing osmotic pressure	It reduces the resistance of the epithelial surface of the oral mucosa to microbial colonization and is also less present in saliva, it is considered a marker of a higher incidence of dental caries.
	MBL2, MASP2	**Mannose binding protein C, mannan-binding lectin serine protease 2** Mediating an immunoglobulin-dependent defence reaction, neutralizing pathogens and facilitating their recognition by phagocytes	Lower resistance to cariogenic bacteria and repeated more severe infections – higher incidence of dental caries with more severe disability.
Genes related to saliva	***CA6***	**Carbonic anhydrase 6** Regulation of pH and buffering capacity of saliva, alkalinisation of saliva	A higher incidence of dental caries with a higher frequency of the genetic variation rs2274327, while with a lower frequency of this variation it is associated with a lower incidence of caries – higher alkalinisation of saliva using carbonic anhydrase and higher resistance to caries.
	MUC7	**Mucin-7** Inhibition of colonization of cariogenic bacteria and reduction of their adhesion on the tooth surface	Higher association with dental caries in genetic variation with reduced expression of mucins.
	AQP5	**Aquaporin 5** Expressed in salivary glands, water transport, regulation of cell osmosis	Increases resistance to caries – affects the amount of saliva production and also interferes with tooth formation – plays a role in the hydration of the extracellular matrix during tooth development.

Tab. 1. (continued)

	GENE	ENCODED PROTEINS AND FUNCTION	ROLE IN CARIES PATHOGENESIS
Genes related to taste	*TAS1R2*	**Taste receptor type 1 member 2 (sweet)** Perception of sweet taste and determination of taste preferences	Determining the degree of sensitivity of the sweet taste perception – lower sensitivity is also related to a higher intake of cariogenic food and thus a higher risk of developing dental caries – association with a higher caries risk
	TAS2R38	**Taste receptor type 2 member 38 (bitter)** Perception of bitter taste and determination of taste preferences	Determining the degree of sensitivity of the bitter taste perception – associated with lower caries risk

Genes involved in the tooth formation, especially genes responsible for enamel formation, are the most studied group of candidate genes for the development of dental caries. These genes are involved in the development of dental caries either by interaction with oral cariogenic bacteria or by influencing the thickness and stage of enamel biomineralization (41, 42).

Enamel is formed by extracellular matrix secretion, ameloblast secretion and mineralization. The cells responsible for enamel formation are called ameloblasts. These cells disappear after the tooth erupts into the oral cavity. The organic extracellular matrix of enamel is formed by enamel proteins and enzymes that regulate the formation of enamel crystals (43).

Ninety percent of these proteins is a heterogeneous group of low molecular weight proteins – amelogenins. Amelogenins are encoded by the AMELX and AMELY genes. The AMELX gene is located on the short arm of the X chromosome (Xp22, 31–p22.1). Males have an equivalent of this gene (AMELY) on the Y chromosome. Mutations of the AMELX and AMELY genes lead to a deficiency of amelogenins and a disorder in the formation of the enamel matrix, which has an abnormal structure, making it prone to fractures and caries (44, 45).

The remaining 10% represents a group of proteins called non-amelogenins, which include: enamelin encoded by the ENAM gene and ameloblastin encoded by the AMBN gene. Tuftelins, encoded by the TUFT1 gene are also involved in the formation of the enamel matrix and, in the early stages of development, also in its mineralization (20, 46). A significant part of tuftelins is secreted at the dentin-enamel interface. Excessive expression of genes encoding tuftelins results in increased production of these proteins and disturbances in the structure of the prisms and the crystalline structure of enamel. Mutations in the genes encoding tuftelins can affect susceptibility to caries (47, 48).

There are other proteins that may be involved in amelogenesis, which we call kallikreins (kallikrein 4 encoded by the KLK4 gene) and matrix metalloproteinases (encoded by the MMP genes). The main role of MMPs and KLK4 in the process of enamel formation is to mediate the replacement of the organic matrix with minerals, thereby creating a mineralized, hard and non-porous layer of enamel. Changes in both MMPs and KLK4 also can lead to congenital enamel defects. Kallikreins belong to the group of serine proteinases. They have role as degradation enzymes during enamel maturation (49, 50).

Matrix metalloproteinases are involved in extracellular processes and degradation of enamel proteins (15). Matrix metalloproteinases are the endopeptidases responsible for the remodelling and degradation of extracellular matrix molecules.

Extracellular matrix molecules are necessary for the maintenance of the cellular homeostasis. They are involved in tissue remodelling, wound healing, and angiogenesis. MMPs also take part in the progression of dental caries by their active role in the degradation of the dentin matrix. Caries development is a dynamic process when the inorganic part of dentin dissolves, demineralizes, and exposes the organic matrix, which is afterwards accessible for bacteria or MMPs degradation (51).

MMP14 protein is expressed on the cell surface of ameloblasts and odontoblasts of the developing tooth. Experimental studies have found delayed tooth eruption in the absence of MMP14. MMP16 is a type 1 transmembrane protein that is also involved in tooth development by regulating ameloblast maturation and enamel formation. MMP10 is capable of the degradation of all components of the extracellular matrix (51). The mentioned author identified 28 SNPs in MMP genes. A significant association was found in two SNPs of MMP16 – rs2046315 and rs10429371. SNP rs2046315 had a very strong association with caries incidence. It is located in the 8q21.3 region near another gene RIPK2 (receptor-interacting serine/threonine-protein kinase). There is not a direct link between this gene and the development of dental caries, but it is known that it is involved in apoptosis and is expressed in the dental pulp (51). The second SNP rs10429371 was also identified in other studies, where it was linked with caries on occlusive surfaces (52–54).

Ecker et al (2017) made a follow-up study aimed at verifying the findings from previous GWAS with the focus on loci on the chromosome 4q21 (55). PKD2, ABCG2 and SCPP genes were identified in this region. Mutations in these genes are associated with dentin or enamel hypoplasia. The involvement of these genes in this area of genome indicates promising results. The SCPP genes determining proteins belonging to the group of dentine extracellular matrix – SPP1, MEPE, IBSP, DMP1 and DSPP – are assumed to be the most promising (55).

Genes encoding SIBLING (small integrin-binding ligand N-linked glycoproteins) proteins, which are involved in biomineralization, are also related to other subgroups of SCPP genes affecting tooth formation – enamel matrix genes AMBN and ENAM. SPP1 encodes osteopontin expressed in multiple tissues. It is involved in mineralization and tissue remodelling. MEPE is an osteoregulin gene and is expressed during odontogenesis. IBSP is a gene encoding bone sialoprotein 2, a component of mineralized tissues, dentin and cementum. DMP1 and DSPP encode dentin matrix acidic phosphoprotein 1 and dentin sialoprotein, both essential

for dentin mineralization, with DMP1 regulating DSPP. DSPP encodes two main proteins of the dentin matrix – sialoprotein and a dentin phosphoprotein. Both are formed by the preproprotein secreted by odontoblasts. Dentin phosphoprotein is involved in the biomineralization of dentin. A defect in this gene results in autosomal dominant disorders such as dentinogenesis imperfecta type I and dentin dysplasia type II. Dentin in these disorders is abnormally soft, which predisposes it to a faster progression of caries (52). Several SIBLING proteins are capable of binding to active matrix metalloproteinases. All these genes are significant candidate genes that may play a role in caries susceptibility. The PKD2 gene encoding polycystin is related to the pathogenesis of caries due to its association with craniofacial features. When this gene is mutated, deviations in craniofacial features occur, resulting in craniofacial and dental defects (55).

The association of the ABCG2 gene, encoding membrane transporter in many tissues, with the formation of dental caries has not been directly proven, but its expression in the dental pulp and in ameloblastic tumours is known. Based on this knowledge, it could play a role in the growth of dental tissues. Mapping genetic variation in the region of chromosome 4 where the PKD2 and ABCG2 genes have their loci brought significant associations with multiple SNPs in this region. The most significant associations were with PKD2, where SNPs rs17013735 and rs11938025 were identified (55).

Another gene involved in the development of hard dental tissues is NEDD9. This gene encodes a neural precursor. It is assumed to mediate integrin-initiated transduction signalling pathways. This gene has many functions, including the regulation of neuronal differentiation, development and migration of neural crest cells. A neural crest signalling disorder leads to both enamel and dentin defects. This fact creates a connection with the occurrence of dental caries. Haworth et al (2018) identified the SNP rs7738851 in the intronic region of the NEDD9 gene (56).

Genes influencing the composition and function of saliva

Homeostasis of the oral cavity and protection of the teeth is ensured by saliva. Genes influencing the composition and function of saliva represent another group of genes that are considered to have an influence on the dental caries development. Emphasis is placed on these proteins carbonic anhydrase 6 encoded by the CA6 gene, mucins encoded by the MUC genes, aquaporins encoded by the AQP genes and proline-rich proteins encoded by the PRH and PRB genes (57, 58).

Carbonic anhydrase 6 is a specific isoenzyme secreted by salivary glands that regulates the buffering capacity and pH of saliva. A higher concentration of carbohydrase 6 in saliva increases its pH, making saliva more alkaline (59). The ability to alkalinize the environment of the oral cavity is an important protective factor in the development of dental caries, and therefore genetic variations of the carbonic anhydrase 6 (CA6) gene may play a role in caries aetiology.

During the identification of SNPs in the CA6 gene, several significant associations with the occurrence of dental caries were found. CA6 expression is associated with better neutralization of acids produced in carbohydrate metabolism. The lower frequency of SNPs rs2274327was in individuals with a higher buffering capacity, that means, bigger resistance to dental caries (60–63).

Mucins (MUC) and proline-rich proteins influence the adhesion of cariogenic bacteria to the tooth surface (15). These proteins are secreted by mucinous salivary glands (sublingual and submandibular glands).

MUC is a group of genes encoding glycoproteins (MUC 1–9). These glycoproteins inhibit the colonization of cariogenic bacteria and reduce their adhesion to the tooth surface (64). Buczkowska-Radlińska et al (2012) found an association between the MUC7 gene and dental caries (65).

Proline-rich proteins are the serous proteins of saliva. They represent about half of serous proteins and 70% of all salivary proteins. Acidic proteins rich in proline are encoded by two genes PRH1 and PRH2. The basic proteins are encoded by PRB1-4 genes. Each gene has several alleles that code for different proteins. They are produced by the parotid and submandibular glands. Interestingly, the submandibular gland contains only proline-rich acidic proteins (66, 67). Expression of proline-rich acidic proteins is higher in caries-free people (68). Differences in the incidence of caries are explained by the polymorphism of PRH1 and PRH2 genes determining acidic proteins rich in proline (69). These genes are located on the short arm of chromosome 12 and indels polymorphism formed by three alleles (Db, Pa and Pif) is located in the exon 3 region of the PRH1 gene. Expression of the Db allele is associated with a higher incidence of dental caries and has been found to enhance biofilm formation (30, 70).

Aquaporins are inner membrane proteins that serve as water channels. They enable the transport of water from or into the cells. They maintain the osmotic parameters of cells.

Thirteen aquaporin isoforms (AQP0-12) have been described (71).

Aquaporin 5 (AQP5) is found in exocrine gland secretions, i.e. also in salivary glands. With AQP5 dysfunction, the ability to produce saliva is reduced. AQP5 disorder has also been reported in people with Sjögren's syndrome. The expression of AQP5 surface of the glandular epithelium membrane is altered or unenabled (71). This phenomenon of reduced saliva production contributes significantly to the development of caries. The gene for AQP5 together with the gene AQP4 (encoding aquaporin 4) are included in the group of genes involved in tooth formation. These genes play a role in the hydration of the extracellular matrix during tooth development (41). Wang et al studied and identified two, rs923911 and rs1996315, SNPs in the AQP5 gene (52). These SNPs in the AQP5 gene were associated with a lower susceptibility to dental caries in all studied phenotypes. The A allele of rs1996315 increases caries resistance.

Genes influencing the immune response

Genetic factors influence and modify the immune response. The human major histocompatibility complex called the HLA system (Human leukocyte antigens) has a very important role in the body's immune response and is controlled by genes located on the short arm of chromosome 6. The link between the HLA

complex and dental caries was determined by the fact that individuals with an acquired or congenital immune deficiency have a higher risk of tooth decay (42). Thus, the polymorphism of HLA molecules can influence the degree of oral colonization and thus susceptibility to caries (1).

Various types of immunocompetent cells are present in normal dental pulp. Human dental pulp contains two kinds of class II MHC antigen-expressing cells: dendritic cells and macrophages. Both dendritic cells and macrophages are believed to participate in the immune defence system in the dental pulp. The HLA-DR-positive cells observed throughout the odontoblast layer were dendritic cells, and their location is ideal for capturing antigens invading the dental tubules. These cells were located, for the most part just beneath the odontoblast layer in erupted intact teeth. In teeth, where caries lesions extended from the enamel into the dentin, an aggregation of HLA-DR-positive cells were observed in the sub-odontoblastic region. Also, the number of the macrophages was increased in the area corresponding to the caries lesion. As the caries lesion advanced, the aggregated cells expanded along the odontoblast layer, and they advanced toward the centre of the pulp. In teeth with early caries and the aggregation of HLA-DR-positive cells and macrophages were observed in the restricted area corresponding to caries lesion, which is suggesting that antigenic materials have already spread into the pulp tissue through dentinal tubules. More advanced caries induced more expanded aggregations of HLA-DR-positive cells and macrophages along the odontoblast layer and sub-odontoblastic area of the pulp. In conclusion, HLA-DR-positive cells were observed along the dentin pulp border corresponding to the caries lesion (72).

The HLA genes involved in the development of dental caries are DR beta 1 (HLA-DRB1) and DQ beta 1 (HLA DQB1) (73). The polyallelic HLA-DRB1 and HLA-DQB1 genes encode proteins expressed on the surface of certain cells of the immune system. Evidence of the link between HLA and dental caries was first described by Bagherian et al (2008), who found an association of HLA genes, especially DRB1*04 (DR4) and DRB1*03 (DR3) alleles, with a high concentration of S. mutans in the oral cavity (74). They revealed that the presence of the HLA DR4 allele increases the risk of early caries in children. A higher concentration of S. mutans was required to trigger specific immunity by T-helper lymphocytes in individuals with HLA DR4 surface antigen, compared to individuals who had HLA DR 1,2,3 or 6 (1, 73). It means that the reactivity of the immune system against S. mutans is reduced in individuals with HLA DR4 antigen. Moreover, there is a connection between lower expression of this antigen and lower secretion of IgA (1,75). Thus, alterations in the HLA complex can modify the immune response to S. mutans (30). The HLA DQB1*02 allele represents a protective marker in susceptibility to dental caries, as it is associated with its lower incidence (76).

Antimicrobial salivary peptides – lactoferrin, β-defensin 1 and mannose-binding lectins can also influence the immune response in association with carious lesion (15). Lactoferrin is an iron-binding glycoprotein and belongs to the group of transferrins. It is synthesized in the salivary, lacrimal, bronchial and mammary glands. The content of lactoferrin in breast milk is relatively high (77). Today, lactoferrin is considered a multifunctional, immunoregulatory protein. In addition, it is resistant to proteolysis, especially in an iron-saturated form. High lactoferrin activity against S. mutans was associated with less severe caries lesions (78). A limitation of lactoferrin is that it does not act against all pathogens (79). Polymorphisms of LTF (the gene encoding lactoferrin) are discussed in several studies. Abbasoğlu et al (2015) identified the SNP rs4547741 associated with a lower incidence of caries and was considered as a protective factor (80). Another SNP rs1126478 was also found in this study was confirmed by Azevedo et al (2010) which found that the A allele is associated with a high incidence of caries and thus lower lactoferrin activity (81).

Defensins are members of a large group of antimicrobial cytotoxic peptides that are indispensable elements of innate immunity. They have various antimicrobial effects – chemotactic activity, stimulation of cytokine (interleukin) production in epithelial cells, degranulation of mast cells and many other (82). There are α-defensins (produced in neutrophils, macrophages, intestine) and β-defensins (from leukocytes and mucosal epithelial cells) (83).

β-defensins are expressed on the surface of the mucous membranes of the oral cavity. β-defensin 1 is encoded by the DEFB1 gene located on chromosome 8. This defensin is involved in the resistance of the epithelial surface to microbial colonization and is present in saliva (84). The association of the DEFB1 gene with dental caries is based on the identification of SNPs associated with increased or decreased susceptibility to caries. Ozturk et al (2010) identified 3 SNPs rs11362, rs1799946 and rs1800972 (85). Whereas the rs11362 variant allele A was associated with a higher incidence of dental caries and the rs1799946 variant allele A with a lower incidence of caries. This study suggested for the first time that the polymorphisms in the DEFB1 gene can be used as potential marker of dental caries. SNP rs11362 was also identified in other studies (86). Higher caries susceptibility of rs11362 is interpreted as a reduced concentration of defensin 1 in saliva. The relatively uniform results of these studies indicate that the rs11362 polymorphism in the DEFB1 gene can in fact be considered a marker of a higher incidence of dental caries (86).

Mannose-binding proteins represent other antimicrobial proteins contained in saliva. Mannose-binding proteins – lectins belong to the group of collectins, which are part of innate immunity. They mediate the binding and neutralization of pathogens by activating complement or facilitating their recognition by phagocytes. Individuals with genetic variation in MBL (mannose binding lectin) gene or in MASP (mannose binding lectin serine peptidase) gene generally have decreased resistance to bacterial infection and are prone to repeating and severe infections (87,88).

Olszowski et al (2012) identified SNPs rs7096206 and rs1800450 in the MBL2 gene and rs72550870 in the MASP2 gene (89). The G allele (rs7096206) had higher expression in individuals with more severe caries lesions, which means that these individuals had lower MBL2 expression in saliva (89).

Genes related to taste

Taste is a sensation, that derives from a chemical reaction between a substrate and taste receptors located in the taste buds

or papillae of the tongue (90). Taste preferences are determined by both genetic and environmental factors (91–93).

The perception of sweet taste is mediated by proteins (receptors) encoded by the genes TAS1R2 and TAS1R3. The perception of bitter taste is associated with the gene TAS2R38. These genes influence eating habits by determining the degree of sensitivity or insensitivity to sweet and bitter taste perception. Based on this, individuals prefer more or less cariogenic diet. Individuals who are hypersensitive to sweet or bitter taste can perceive these tastes more intensively even at a lower concentration of the substrate. If we are talking about sweet taste, individuals with this genetic predisposition feel sweet taste at a lower concentration, meaning that the rate of consumption of cariogenic food is lower compared to individuals whose sweet taste receptors have a lower sensitivity. Through this indirect mechanism, the intake of cariogenic food and the risk of dental caries are lower (15, 62, 93, 94).

In general, individuals who have a high sensitivity for specific taste and a low taste threshold perceive this taste at a significantly lower concentration of the substrate. On the other hand, individuals who are not so sensitive to the specific taste, and their sensitivity threshold is therefore higher, need a higher concentration of the substrate for its perception. This may explain the susceptibility to a higher intake of sweet foods and higher incidence of caries in individuals who are less sensitive to sweet taste. The determination of sensitivity to sweet taste can be helpful in estimating individual caries risk (62, 93, 95–98).

The congenital autosomal recessive disease – fructose intolerance is an example of the genetics influence on food intake, and thus the susceptibility to tooth decay. The disease is caused by a deficiency of fructose-1-phosphatase aldolase. After consuming fructose, individuals with this disease suffer from serious somatic symptoms. For this reason, these patients avoid sweet food, which leads to a low incidence of caries lesions (30, 42, 99).

The most important study suggesting correlation of the genetic influence on taste perception with dental caries studied three candidate genes TAS2R38, TAS1R2 and GNAT3 (93). They identified rs713598, rs1726866 and rs10246939 in TASR38 gene, rs4920566, rs9701796 in TAS1R2 gene and rs2074674, rs6962693 in GNAT3 gene. The result of the study was that the C allele of the rs9701796 in the TAS1R2 gene was associated with incidence of caries. The TAS2R38 gene SNPs were associated with a low incidence of caries, and no significant association was found with the GNAT3 gene. Alleles of the bitter taste gene TAS2R38 are protective, while alleles of the sweet taste gene TAS1R2 are non-protective (1). The same SNP rs713598 in TAS2R38 was identified by Yildiz et al (2016), who described that the GG genotype occurred more often in individuals with low caries risk (62). Robin et al (2015) identified two SNPs, one in the TAS1R2 gene (rs3935570) and one in the gene encoding GLUT2 (rs1499821), and found that both were associated with a higher incidence of dental caries (98). Similar results were also concluded in the study by Kulkarni et al (2013) (91). Genetically determined taste preferences were also confirmed by the study in which associations between eating habits and sweet taste recognition in monozygotic and dizygotic twins were examined (100). They confirmed that taste preferences were more similar in monozygotic twins compared to dizygotic twins (101, 102).

Taste preferences are clearly modified by an individual's genetic background and play a significant role in the development of eating habits.

Identification of new genes involved in dental caries

The development of molecular biology and the introduction of new DNA sequencing techniques have significantly contributed to the identification and mapping of genes. Experimental animal models and large-scale whole-genome studies helped to obtain new information for the identification of suspect genes associated with the development of dental caries (15,30). Many associations are awaiting confirmation.

Suspected genes determined by genome-wide association and linkage studies can be classified into two groups. The first group consists of genes that intervene in the modulation of the immune system and the second group of genes is involved in the morphogenesis of teeth.

Suspected genes with immunomodulating potential with a possible association to dental caries are: PART1 gene interfering with the modulation of the colonization of cariogenic microorganisms (103); the BTF3 gene encoding a transcription factor associated with the immune factor NFKB, which has an antimicrobial effect on cariogenic microorganisms (103); the SPRY2 gene involved in immune responses to pathogens present in the oral region (104); the NR3C1 gene encoding the glucocorticoid receptor, which reduces the defence response of odontoblasts upon increased glucocorticoid stimulation (105); the MPPED2 gene associated with oral bacterial colonization (106); RPS6KA2 PTK2B genes involved in the regulation of inflammation and macrophage activity (52); LYZL2 gene associated with antibacterial effect (54); genes CXCR1, CXCR2 determining chemokine receptors (53); the ITGAL gene encoding alpha L integrin essential for proper leukocyte intercellular adhesion; the PLUNC gene group with a potential role in defence against oral pathogens (107); IL32 gene encoding interleukin 32 (108); the CTSC gene responsible for the synthesis of cathepsin C, which participates in various immune and inflammatory reactions, activates phagocytes and T-lymphocytes, maintains the function of NK cells (109–112); NCF2 gene determining neutrophil cytosolic factor; the CSF1R gene encoding colony-stimulating factor receptor 1 and the STAB1 gene determining stable protein 1, which control the production, differentiation and function of macrophages (111) and the CELF4 gene associated with a higher incidence of caries and the presence of S. mutans (108); BMP7 gene encoding bone morphogenetic protein 7 involved in tissue mineralization and tooth and enamel development (113).

Suspected genes that are involved in tooth morphogenesis are: ZSWIM6 gene (103); ACTN2 gene involved in enamel formation (106); the EDARADD gene, the mutation of this gene leads to abnormal tooth development (56,106); the RHOU gene encoding GTPases and the FZD1 gene both involved in the Wnt signalling cascade (52); the ISL1 gene, expressed in epithelial

Tab. 2. The list of all suspected genes.

	GENE	ENCODED PROTEIN AND FUNCTION	SUSPECTED ROLE IN CARIES PATHOGENESIS
Suspected genes involved in tooth morphogenesis	***ISL1***	**Insulin gene enhancer protein ISL-1** A transcription factor playing a role in embryogenesis and neuronal differentiation.	In experimental studies, the gene is expressed only in the epithelial cells of the developing incisors, and is an important regulatory factor in the development of the sled, jaw and teeth.
	FZD1	**Frizzled-1** Receptor of molecules of the Wnt signalling pathway.	Responsible for the activation of intracellular signals of the Wnt pathway for the initiation of tooth eruption.
	RHOU	**Rho-related GTP-binding protein RhoU** GTPases are mediators of the Wnt signalling cascade, which is involved in the regulation of tooth morphology during dentition.	Potentially influencing dentition development.
	AJAP1	**Adherens junction-associated protein 1** It plays a role in cell adhesion and migration.	A potential role of the gene lies in the regulation of dentition. The gene is mainly associated with the development of dental caries of premolars and canines.
	BCOR	**BCL-6 corepressor** A key transcriptional regulator during embryogenesis, expressed in dental tissue, essential for tissue differentiation	Mutations in this gene lead to oculofaciocardiodental syndrome, which is accompanied by dental abnormalities. Decreased expression of the gene leads to dentinogenesis defects and delayed tooth root development and eruption.
	INHBA	**Inhibin beta A chain** Gene expression in mesenchymal cells responsible for tooth development is essential for tooth bud formation.	Decreased expression in experimental studies resulted in impaired eruption of incisors and mandibular molars.
	BCORL1	**BCL-6 corepressor-like protein 1** Repressor of transcription	Associated with caries of smooth surfaces. Its role in the development of dental caries was suspected because of its similarity to the BCOR gene.
	ADAMTS3	**A disintegrin and metalloproteinase with thrombospondin motifs 3** Maturation of fibrous collagen type II. Activation of the lymphangiogenic factor for the development and growth of lymphatic vessels.	The exact role in cariogenesis is not yet fully elucidated, but in experimental studies it was significantly expressed in the dental papilla during tooth development.
	GALK2	**N-acetylgalactosamine kinase** Phosphorylation of galactose.	Lower expression of GALK2 leads to reduced N-acetylgalactosamine kinase activity, which ultimately leads to increased metabolism of galactose by plaque bacteria and higher acid production and decreased plaque pH.
	ZSWIM6	**Zinc finger SWIM domain-containing protein 6** Responsible for the development of the nervous system.	Its mutation responsible for acromelic frontonasal dysostosis
	CCNB1	**G2/mitotic-specific cyclin-B1** Regulatory protein involved in mitosis, maturation-promoter factor.	Expressed in saliva and salivary glands.
	NAMPT	**Nicotinamide phosphoribosyltransferase** Pro-inflammatory adipokine.	The function in cariogenesis is not entirely clear, the probable connection of this gene is related to the regulation of degradative matrix metalloproteinases.
	BMP7	**Bone morphogenetic protein 7** Growth factor involved in the mineralization of tissues and the development of teeth and enamel.	Absences of BMP7 in experimental studies resulted in dental and salivary defects
	IL32	**Interleukin-32** Part of the pro-inflammatory cytokine group.	Higher IL32 expression associated with higher levels of caries severity in the presence of S. mutans.
	ACTN2	**Alpha-actinin-2** Present in the cytoskeleton of ameloblasts	Involvement in enamel formation – organization of ameloblasts during amelogenesis
	MTR	**Methionine synthase** Production of methionine and homocysteine; involved in the development of orofacial features.	It may contribute to the development of non-syndromic cleft lip and palate, which is associated with a higher incidence of dental caries.
	EDARADD	**Ectodysplasin-A receptor-associated adapter protein.** Development of ectoderm derivatives, expression in epithelial cells.	Its mutation causes hypohydrotic ectodermal dysplasia, which leads to abnormal development of teeth, skin, hair, nails and sweat glands
	LPO	**Lactoperoxidase** An enzyme that plays a role in the metabolism of bacteria.	Inhibition of plaque formation and gingivitis.
	ESRRB	**Steroid hormone receptor ERR2** Estrogen receptor-like protein.	The depressant function of oestrogens to secrete growth hormone from the adenohypophysis, which is closely related to the development and maintenance of the normal histological structure of the salivary glands.

Tab. 2. (continued)

	GENE	ENCODED PROTEIN AND FUNCTION	SUSPECTED ROLE IN CARIES PATHOGENESIS
Suspected genes related to immunomodulatory potential	***PART1***	**Long non-coding RNAs with non-systematic symbols** Gene not coding for any protein, its involvement in prostate carcinogenesis is assumed.	Expression in saliva, interactions with immune response factors and modulation of colonization by cariogenic microorganisms
	BTF3	**Transcription factor BTF3** Required for transcription initiation.	Expressed in saliva and salivary glands, expression associated with the immune factor NFKB.
	SPRY2	**Protein sprouty homolog 2** Expression in epithelial cells, regulation of epidermal growth factor.	Involvement in immune reactions against pathogens, in the control of the integrity of the oral mucosa and has a mitogenic effect on the salivary glands.
	NR3C1	**Glucocorticoid receptor** Glucocorticoid sensitive receptor.	Reduction of the defence response of odontoblasts during increased glucocorticoid stimulation.
	MPPED2	**Metallophosphoesterase MPPED2** Potential role in nervous system development.	Involvement in response to oral bacterial colonization is hypothesized. Associated with the development of caries of the occlusal surfaces of the teeth.
	RPS6KA2	**Ribosomal protein S6 kinase alpha-2** Enzyme catalysing the phosphorylation of components of the MAPK (mitogen-activated kinase) signalling pathway, involved in the control of cell growth and differentiation	Activation of the MAPK signalling pathway plays an important role in the regulation of inflammatory cytokine and chemokine genes. From this, it is assumed that RPS6KA2 is also involved in diseases of the oral cavity such as dental caries.
	PTK2B	**Protein-tyrosine kinase 2-beta** Mediation of MAPK signalling pathway, role in regulation of humoral immune response; regulation of cytoskeleton reorganization, cell polarization, migration, adhesion and bone remodelling.	It has a role in the inflammatory response for normal macrophage polarization and migration. In the pathogenesis of dental caries, it is assumed to be widely involved in the mediation of the immune response and the mediation of the MAPK signalling pathway.
	LYZL2	**Lysozyme-like protein 2** C-type lysozyme – bacteriolytic factor.	An antibacterial function is assumed, which could be involved in cariogenesis. A gene mainly involved in the development of dental caries of the lower frontal teeth.
	CXCR1, CXCR2	**C-X-C Chemokine receptors** Major receptors for IL8 (a chemokine that is an essential mediator of the inflammatory response), Increased expression of IL8 is present in inflamed dental pulp.	The expression of these receptors has been associated with the presence of certain periodonto-pathological bacteria in the inflamed gingival tissue. Their influence in the development of tooth decay consists in affecting the individual‘s susceptibility to oral bacteria. The association of these genes was with caries of smooth tooth surfaces.
	ITGAL	**Integrin alpha-L** Expressed on all leukocytes, it plays a role in leukocyte intercellular adhesion and stimulation of lymphocyte signalling.	ITGAL expression is increased in CD4(+) and CD8(+) T cells in chronic and aggressive periodontitis. It is also believed to affect the development of tooth decay.
	PLUNC (BPIFA1)	**BPI fold-containing family A member 1** Involvement in innate immunity against pathogens in the oral and nasal cavity.	Expressed in salivary glands and oral cavity. Potential role in defence against oral pathogens.
	CTSC	**Dipeptidyl peptidase 1** A lysosomal enzyme that degrades proteins, activates enzymes, participates in various immune and inflammatory reactions, activates phagocytes and T-lymphocytes, maintains the function of NK cells.	Responsible for the functions of NK cells that are present in healthy dental pulp. Alteration of this gene increases the frequency of dental pulp infection. Mutations also lead to Papillon-Lefevre syndrome associated with severe caries and periodontitis.
	NCF2	**Neutrophil cytosol factor A** Component of NADPH oxidase that generates superoxide, reactive oxygen radicals designed to kill bacteria by neutrophils.	Neutrophils are the first inflammatory cells present in the dental pulp when it is damaged. They play an important role in resistance to the development of dental caries and its penetration into the dental pulp.
	STAB1	**Stabilin-1** Induction of macrophage expression during chronic infection	The dental pulp contains a large number of macrophages, which are among the immunocompetent cells that resist caries bacteria.
	CELF4	**CUGBP Elav-like family member 4** Maintenance of mRNA stability and availability in excitatory neurons; regulation of synaptic plasticity and transmission.	Obesity has been observed in CELF4 mutation in experimental studies. It is obesity that has a possible connection with tooth decay. A connection with a higher incidence of caries, this gene and the presence of S.mutans was also found.
	CSF1R	**Macrophage colony-stimulating factor 1 receptor** A membrane receptor that controls the production, differentiation and function of macrophages. Mediation of almost all biological effects of cytokines.	Macrophages are an important part of the dental pulp‘s line of defense in case of damage and penetration of bacteria from the caries deposit.

cells of developing incisors (56); the AJAP1 gene encoding protein 1, which is involved in the regulation of dentition (107); the INHBA gene essential for tooth bud formation (107); the BCOR gene determining the BCL6 co-repressor essential for tissue differentiation (53) and the NAMPT gene encoding a nicotinamide phosphoribosyltransferase capable of regulating degradative matrix metalloproteinases (56). The gene for estrogen receptor beta is also included in this group, it may be related to the development and maintenance of the normal histological structure of the salivary glands (104).

The list of all suspected genes can be found in Table 2.

Conclusion

Dental caries is a multifactorial disease caused by both genetic and great deal of environmental factors. The aetiology of caries is very complex and the identification of a specific causative agents and understanding of their combined effect requires implementation of new stand points and employment of artificial intelligence.

In this review, we accomplished to prove the genetic component in the aetiology of dental caries, to offer the clear classification and description of the function of the genes involved in its formation. The genes involved in the development of dental caries are divided into four basic groups – genes playing a role in the formation and development of hard dental tissues, genes affecting the composition and amount of saliva, genes involved in the immune response to cariogenic microorganisms and genes involved in taste and food preferences.

The identification of new genes brings better understanding of this complex disease and its aetiology. Further investigation of these genes and genetic variations is necessary to better understand the mechanism of action and involvement in the caries development.

In the future, genetics could play a key role in estimating the risk of dental caries in everyone. This would significantly improve the prevention, prognosis and therapy of dental caries.

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