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Single Nucleotide Polymorphism in the Aetiology of Caries: Systematic Literature Review

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Abstract
Recent progress in the field of molecular biology and techniques of DNA sequence analysis allowed determining the meaning of hereditary factors of many common human diseases. Studies of genetic mechanisms in the aetiology of caries encompass, primarily, 4 main groups of genes responsible for (1) the development of enamel, (2) formation and composition of saliva, (3) immunological responses, and (4) carbohydrate metabolism. The aim of this study was to present current knowledge about the influence of single nucleotide polymorphism (SNP) genetic variants on the occurrence of dental caries. PubMed/Medline, Embase, and Cochrane Library databases were searched for papers on the influence of genetic factors connected with SNP on the occurrence of dental caries in children, teenagers, and adults. Thirty original papers written in English were included in this review. Study groups ranged from 30 to 13,000 subjects. SNPs were observed in 30 genes. Results of the majority of studies confirm the participation of hereditary factors in the aetiology of caries. Three genes, *AMELX*, *AQP5*, and *ESRRB*, have the most promising evidence based on multiple replications and data, supporting a role of these genes in caries. The review of the literature proves that SNP is linked with the aetiology of dental caries.

Dental caries is a complex, multifactorial illness which still appears to be one of the most common among human beings, in spite of the application of various preventive methods [Petersen, 2003]. Genetic and environmental factors, which mutually influence one another, take part in the development of caries. Their identification and knowledge of the mechanisms of influence have important meaning in the full understanding of the essence of carious disease [Wang et al., 2012b; Opal et al., 2015]. In the past century scientists became widely interested in the effect of hereditary factors on the risk of caries development. Examinations in order to explain the potential impact of genetics on caries risk at various organisms were conducted. The development of molecular biology and techniques of DNA sequence analysis initiated more advanced and reliable studies, proving the role of hereditary features in the occurrence of dental caries [Shuler, 2001;

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Vieira, 2012]. There has also been considerable progress in the mapping of the human genome, which presents the position of particular genes on the chromosome. Therefore, the identification of genes contributing to increased caries susceptibility became possible [Werneck et al., 2010]. Studies of genetic mechanisms in the aetiology of caries encompass, primarily, 4 main groups of genes responsible for (1) development of the enamel, (2) formation and composition of saliva, (3) immunological response, and (4) carbohydrate metabolism [Shuler, 2001; Darshana et al., 2014]. Genome-wide scan studies conducted by Vieira et al. [2008] revealed the association of loci 5q13.3, 14q11.2, and Xq27.1 with low caries vulnerability, which was confirmed later by Shimizu et al. [2013] and Küchler et al. [2014]. On the other hand, loci 13q31.1 and 14q24.3 were connected with high caries susceptibility [Vieira et al., 2008]. Other genome-wide association studies (GWAS) suggested some loci within or near genes *RPS6KA2* (chromosome 6), *PTK2B* (chromosome 8), *RHOU* (chromosome 1), *FZD1* (chromosome 7), and *ADMTS3* and *TLR2* (chromosome 4), as well as *ISL1* (chromosome 5), *ACTN2* (chromosome 1), *MTR* (chromosome 1), and *AJAP1* (chromosome 1), which can probably participate in caries development in permanent or primary dentition [Shaffer et al., 2011; Wang et al., 2012a; Shaffer et al., 2013]. Recently published GWAS by Morrison et al. [2016] conducted in a Hispanic population suggested associations in genes lacking known or plausible roles in dental caries, for example, the *NAMPT* gene (which is involved in many biological processes including periodontal healing) and the *BMP7* gene (involved in dentin development) in the carious process. Genetic research studies concerning single nucleotide polymorphism (SNP) are positively more popular, as SNP is the most common form of human genome variability [Yang et al., 2014; Jiang et al., 2016]. The aim of this literature review was to present current knowledge about the influence of SNP genetic variants on the occurrence of dental caries.

Materials and Methods

PubMed/Medline, Embase, and Cochrane Library databases were searched for candidate gene studies on the influence of SNP genetic variants on the occurrence of dental caries using the following protocol: "dental caries susceptibility/genetics" (Medical Subject Headings, MeSH). Additionally, subsequent key words were used: "caries genetics," "caries single nucleotide polymorphism," "caries SNP," "caries genetic aetiology," and "dental caries genes." The search was complemented manually by references of the most recent pertinent reviews and original articles. The titles of the papers were verified, duplicates were excluded, and significant abstracts and, subsequently, papers were chosen and downloaded in full text. Inclusion criteria were up-to-date original papers – candidate gene studies concerning children, teenagers, or adults in which SNPs were related to genes responsible for (1) development of the tooth, (2) formation and composition of saliva, (3) host immunological response, and (4) carbohydrate metabolism. Exclusion criteria were case reports, studies on animals, and genetic studies on aspects other than SNPs (e.g., microsatellite markers, biochemical markers). The quality of the original studies was assessed using the Newcastle-Ottawa Scale (NOS).

Results

Out of 2,551 obtained records, 30 papers qualified for the review of the literature. The schema of the qualification process is presented by a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram (Fig. 1).

Out of the 30 qualified papers, 21 studies reported statistically significant associations between genes associated with caries and SNPs. Study groups range from 30 to nearly 13,000 subjects. SNP was observed in 30 genes. The issue of the development of the tooth was raised in 17 papers, the formation and composition of saliva in 7, host immunological response in 7, and carbohydrate metabolism in 5. Some papers focused on SNP in 1 gene, others on SNPs in several genes. In the majority of the quoted researches caries was evaluated using the DMFT/DMFS index for permanent dentition and the dmft/dmfs index for primary dentition, excepting Duverger et al. [2014] (caries presence/absence), Fine et al. [2013] (X-ray evaluation), and Fushan et al. [2009] (no caries evaluation). The age range of the patients was from 1 to 84 years (9 studies considered children, 9 adults, and 11 both children and adults). The results show the studied population (homogeneous vs. heterogeneous), the selected statistical approaches (univariate vs. multivariate analyses), and haplotype combination.

An overview of the study results is described in Tables 1–4. Table 1 reports results of studies concerning genes taking part in tooth formation. Results of studies regarding genes influencing the composition and functions of saliva are introduced in Table 2. Results of studies related to genes influencing the immune response are shown in Table 3. Table 4 reports results of studies concerning genes influencing carbohydrate metabolism. The quality of the included studies, assessed using the NOS, is shown in Table 5. The highest quality studies were awarded up to 8 stars (9 out of 30 studies).

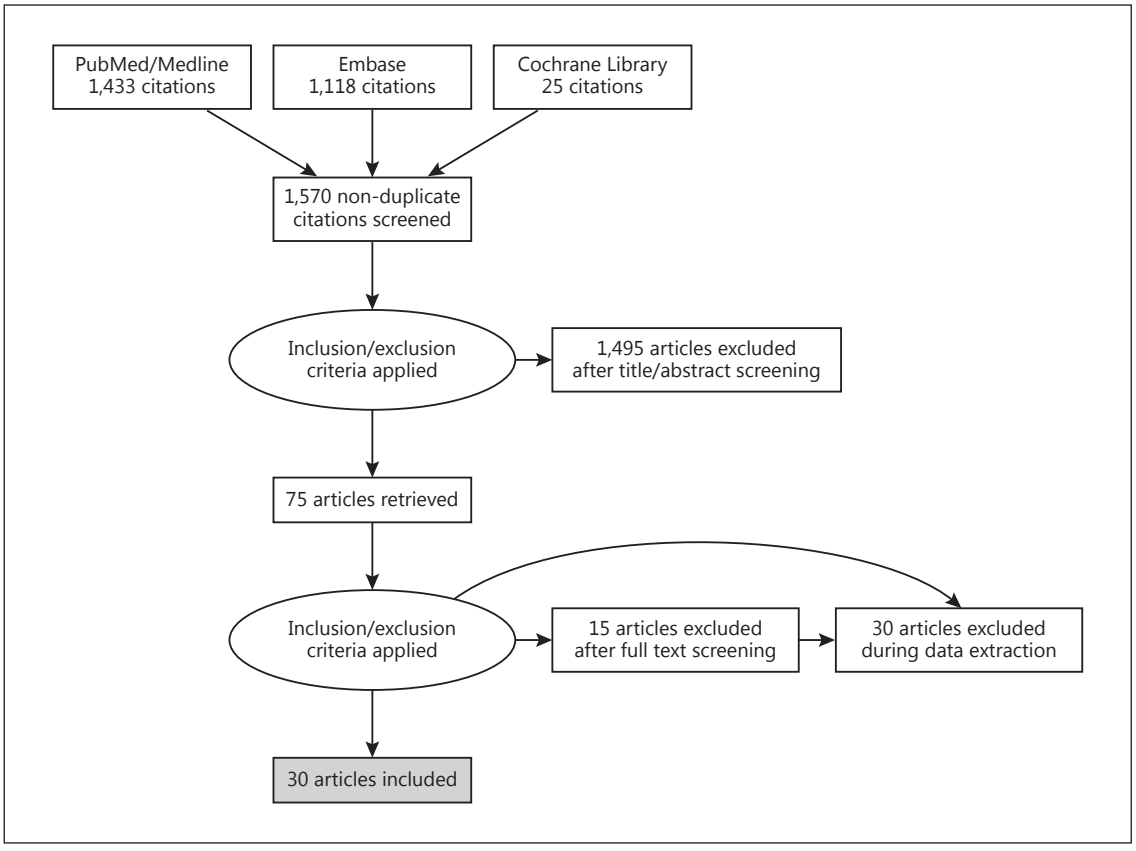

Fig. 1. PRISMA flow diagram.

Discussion

Evidence on the influence of genetic factors on the occurrence of dental caries generally comes from research studies concerning 4 main groups of genes taking part in the development of the enamel, formation and composition of saliva, immunological response, and carbohydrate metabolism. However, recent studies revealed that they can also come from other genes that previously were not expected to modulate the carious disease.

Authors of some studies included in the review observed the SNP phenomenon in genes involved in amelogenesis [Slayton et al., 2005; Deeley et al., 2008; Patir et al., 2008, 2014; Kang et al., 2011; Olszowski et al., 2012; Shimizu et al., 2012; Tannure et al., 2012a, b; Wang et al., 2012b; Gasse et al., 2013; Chaussain et al., 2014; Duverger et al. 2014; Abbasoğlu et al., 2015; Anjomshoaa et al., 2015; Shaffer et al., 2015; Yildiz et al., 2016]. Amelogenesis is a genetically controlled process of enamel development. Two main groups of proteins take part in the process: amelogenins (encoded by *AMELX* and *AMELY* genes) and non-amelogenins – enamelin (encoded by the *ENAM* gene), ameloblastin (encoded by the *AMBL* gene), and tuftelin (encoded by *TUFT1* or *TFIP11* genes). There are also other proteins which can assist in amelogenesis, like kallikreins (e.g., kallikrein 4 encoded by the *KLK4* gene) or metalloproteinases (e.g., metalloproteinase 13, encoded by *MMP13*, and metalloproteinase 20, encoded by *MMP20*) [Werneck et al., 2010; Opal et al., 2015]. The results of the quoted research studies indicate that different gene variants, connected with SNP, can be linked to higher as well as lower caries vulnerability. Patir et al. [2008] proved that increased caries susceptibility is connected with allele T of tuftelin (rs3790506) and allele C of amelogenin (rs17878486). The authors emphasize that the connection of tuftelin's SNP with dental caries revealed in the study does not depend on simultaneous analysis of *Streptococcus mutans* infection. Such reliance was observed earlier by Slayton et al. [2005]. On the other hand, a possible interaction of *S. mutans* infection with enamelin variants was noticed. Abbasoğlu et al. [2015] remarked the relation of some SNPs (kallikrein 4 –

Table 1. Overview of studies concerning genes taking part in tooth formation

Authors, year	Study population (HO/HE), *n*, age, years	Examples of examined genes: SNP/MAF	Results	Statistical approaches
Morrison et al., 2016	HO 12,803 18–74	*BMP7*: rs72626594/0.01(A)	Significant influence on caries risk	MA $p = 3 \times 10^{-8}$
Yildiz et al., 2016	HO 154 20–60	*AMELX*: rs6639060/0.46(T)	No influence on caries occurrence	MA Not significant $p > 0.05$
Abbasoğlu et al., 2015	HO 259 4.6±0.61	*ENAM*: rs1264848/0.11(C) *KLK4*: rs198968/0.32(A) *TUFT1*: rs3790506/0.25(A)	GG genotypes protective for ECC	MA $p = 0.032$ MA $p = 0.040$ UA, MA $p = 0.014$
		ALOX15: rs7217186/0.47(T)	TT genotype is a risk factor for ECC	MA $p = 0.050$
Anjomshoaa et al., 2015	HE 1,383 2–84	*AQP5*: rs3759129/0.08(C) rs467323/0.35(T) rs1996315/0.43(A) rs10875989/0.48(C)	Significant influence on caries experience Haplotype rs461872-rs1996315 (dominant model) Haplotype rs3759129-rs1996315 (recessive model)	MA $p = 0.03$ $p = 0.01$
Shaffer et al., 2015	HE 3,600 3–12 18–79	*TUFT1*: rs2337359/0.47(C)	Significant relation with caries in adults; no SNPs showed association in both children and adults	MA $p < 0.002$
		TUFT1: rs2337359/0.47(C) *AMBN:* rs7439186/0.12(T)	Relation of SNP variant with type of fluorine exposure	MA $p < 0.05$
Chaussain et al., 2014	HO 358 7.6±2.9 22.0±1.8	*ENAM*: rs2609428/0.04(C) rs7671281/0.12(C) rs3796704/0.10(A)	rs2609428 associated with caries (OR, 3.89; 95% CI, 1.47–10.33) Haplotype rs7671281-rs3796704 associated with caries (OR, 2.66; 95% CI, 0.99–7.20)	UA $p < 0.05$ MA $p < 0.05$
Duverger et al., 2014	HO 1,092 6–12 25–50	*KRT75*: rs2232387/0.14(T)	Allele A increases caries susceptibility	UA $p = 0.0175$
Gasse et al., 2013	HE 358 2–17	*AMELX*: rs184371797/0.001(C) rs946252/0.30(T) rs200163085/0.01(G)	No influence on caries occurrence	UA, MA Not significant $p > 0.05$
Olszowski et al., 2012	HO 179 5, 13	*AMELX*: rs2106416/0.16(T)	No influence on caries occurrence	UA Not significant $p > 0.05$

Table 1 (continued)

Authors, year	Study population (HO/HE), *n*, age, years	Examples of examined genes: SNP/MAF	Results	Statistical approaches
Shimizu et al., 2012	HE 1,831 1–82	*AMELX:* rs946252/0.31(T) *TUFT1:* rs4970957/0.22(G) *AMBN:* rs4694075/0.48(C) *ENAM:* rs12640848/0.33(G)	Allele T (rs946252) and allele C (rs4694075) increase caries susceptibility	MA $p = 0.01$ $p = 0.007$
Tannure et al., 2012b	HE 388 9.03±2.75	*MMP20:* rs1784418/0.42(T)	Allele T may increase caries risk	MA Not significant $p > 0.05$
Tannure et al., 2012a	HE 505 3–21	*MMP13:* rs2252070/0.36(C)	GG genotype increases caries risk	MA $p = 0.004$ (OR, 0.538; 95% CI, 0.313–0.926)
Wang et al., 2012b	HE 333 4–7	*DSPP:* rs2615487/0.32(T) *KLK4:* rs2235091/0.36(G)	Allele A (rs2235091) and allele T increase caries resistance	MA $p < 0.05$
Kang et al., 2011	HE 120 22.7±7.8	*AMELX:* rs17878486/0.08(C) rs5933871/0.27(C) rs5934997/0.27(C)	TT genotypes (rs5933871; rs5934997) increase caries susceptibility	MA $p = 0.001$ $p = 0.000$
Deeley et al., 2008	HO 110 7–14	*AMBN:* hCV496502/0.22(T) *AMELX:* hCV2190967/0.06(T)	Variants of amelogenin gene are connected with higher caries susceptibility	UA $p = 0.0000001$
Patir et al., 2008	HO 173 4.82±0.81	*AMBN:* rs34538475/0.17(T) *AMELX:* rs178784860.08(C) *TUFT1*: rs3796704/0.14(A) *ENAM:* rs3790506/0.25(A)	Allele T (rs3790506) and allele C (rs17878486) increase caries susceptibility	MA $p = 0.05$ $p = 0.01$
Slayton et al., 2005	HE 470 3–5	*TUFT1:* CTTCTCAAGGT/CTG-TAGGAAGA /0.26(A)	Variants of tuftelin gene connected with high *S. mutans* quantity may predispose to caries	MA Not significant $p > 0.05$

HO, homogeneous; HE, heterogeneous; ECC, early childhood caries; UA, univariate analysis; MA, multivariate analysis; MAF, minor allele frequency.

rs198968, enamelin – rs1264848, lactoferrin – rs4547741, and tuftelin – rs3790506) with decreased caries susceptibility. Particular genotypes in the examined patients were determined as protective against early childhood caries. Similar results were achieved by Wang et al. [2012b], who created a comparison of alleles, which predispose to a decreased risk of smooth surfaces or pit/fissure caries, after they analysed polymorphic variants of genes (*KLK4* – rs2235091, *DSPP* – rs2615487, and *AQP5* – rs1996315). Different results were obtained by Olszowski et al. [2012]

Table 2. Overview of studies concerning genes influencing composition and functions of saliva

Authors, year	Study population (HO/HE), *n*, age, years	Examples of examined genes: SNP/MAF	Results	Statistical approaches
Yildiz et al., 2016	HO 154 20–60	*CA6*: rs2274327/0.27(T)	Allele T less frequent in patients with high buffer capacity	MA $p < 0.05$
Li et al., 2014	HO 355 51.16±9.48	*CA6*: rs2274328/0.50(A) rs17032907/0.22(T) rs11576766/0.35(C) rs2274333/0.34(G) rs10864376/0.47(C) rs3765964/0.46(A) rs6680186/0.40(G)	Haplotype ACA (rs17032907) can be connected with higher caries susceptibility	MA Not significant $p > 0.05$
Buczkowska-Radlińska et al., 2012	HO 158 20–21	*MUC7*: Exon 3/0.22	No influence on caries intensity	UA Not significant $p > 0.05$
Koç Öztürk et al., 2012	HO 43 45.3±13.5	*CA6*: rs2274327/0.27(T) rs2274328/0.50(A) rs2274329/0.09(C)	Positive correlation with CA6 activity	UA $r = 0.427$ $p < 0.05$
Wang et al., 2012b	HE 333 4–7	*AQP*: rs923911/0.22(A) rs1996315/0.43(A)	Allele A increases caries resistance GC haplotype protective for caries GG haplotype is risk for caries	MA $p < 0.05$ $p = 0.02$ $p = 0.03$
Yarat et al., 2011	HO 44 21.95±2.2	*CA6*: dbSNP 142460367/0.02(A) 142460368/0.01(A)	No influence on caries susceptibility	UA Not significant $p > 0.05$
Peres et al., 2010	HO 245 7.84±0.81	*CA6*: rs2274327/0.27(T) rs2274328/0.50(A) rs2274333/0.34(G)	TT genotype (rs2274327) less frequent in high buffer capacity	UA $p = 0.023$

HO, homogeneous; HE, heterogeneous; UA, univariate analysis; MA, multivariate analysis; MAF, minor allele frequency.

and Yildiz et al. [2016], who failed to prove any connection of SNP of amelogenesis genes with dental caries vulnerability. There is a possibility that it was caused by inappropriate SNP selection (minor allele frequency in the population) or too small a number of SNPs checked for 1 gene. In contrast to authors focusing on amelogenesis, Morrison et al. [2016] noted the occurrence of SNP in genes stimulating the development of dentin *(BMP7)*, which was not previously mentioned in the literature.

Various components of saliva influence its different functions, which contribute to maintaining oral homeostasis and tooth protection. Carbonic anhydrase 6 is a salivary enzyme which is assigned to regulate the buffer capacity and pH of saliva. Mucins and proline-rich proteins take part in bacteria cell agglutination, including cariogenic bacteria [Darshana et al., 2014; Opal et al., 2015]. Researchers examined SNP in genes encoding salivary components – *CA6* (for carbonic anhydrase 6), *MUC 7* (for mucin), *AQP* (for aquaporin), and *PRH1* (for proline-rich protein 1) [Peres et al., 2010; Yarat et al., 2011; Buczkowska-Radlińska et al., 2012; Koç Öztürk et al., 2012; Wang et al., 2012b; Li et al., 2015; Yildiz et al., 2016].

Table 3. Overview of studies concerning genes influencing immune responses

Authors, year	Study population (HO/HE), *n*, age, years	Examples of examined genes: SNP/MAF	Results	Statistical approaches
Yildiz et al., 2016	HO 154 20–60	*DEFB1*: rs11362/0.40(T)	Allele A more frequent in high caries risk	MA $p = 0.000$
Abbasoğlu et al., 2015	HO 259 4.6±0.61	*LTF*: rs4547741/0.07(T) *BEFB1*: rs11362/0.40(T)	CT genotype (rs4547741) is a protective factor for ECC	UA, MA $p = 0.038$
Krasone et al., 2014	HO 69 2–12	*DEFB1*: rs11362/0.40(T) rs1800972/0.14(C)	CC genotype (rs11362) connected with high caries susceptibility	UA $p = 0.031$ (OR, 3.16; 95% CI, 0.97–10.62)
Fine et al., 2013	HE 30 34.6±9.1	*LTF*: rs1126478/0.37(T)	Variant LTF/K connected with high lactoferrin activity against *S. mutans* and low caries intensity	UA $p = 0.02$ (RR, 3.6; 95% CI, 1.5–11.13)
Olszowski et al., 2012	HO 179 5 and 13	*MBL2*: rs7096206/0.20(G) rs1800450/0.12(T) *MASP2:* rs72550870/0.01(C)	Allele G (rs7096206) more frequent in high caries intensity	UA Not significant $p > 0.05$
Azevedo et al., 2010	HO 110 12	*LTF*: rs1126478/0.37(T)	Allele A connected with high caries susceptibility	UA $p = 0.01$ (OR, 0.16; 95% CI, 0.03–0.76)
Ozturk et al., 2010	HE 296 17–84	*DEFB1*: rs113620.40(T) rs179946/0.42(A) rs1800972/0.14(C)	Haplotype GCA connected with high caries intensity Haplotype ACG connected with low caries intensity	MA $p = 0.0023$, (OR, 2.19; 95% CI, 1.1–4.35) $p = 0.0010$

HO, homogeneous; HE, heterogeneous; ECC, early childhood caries; UA, univariate analysis; MA, multivariate analysis; MAF, minor allele frequency.

The relation of the *CA6* gene with the buffer capacity of saliva was observed by Yildiz et al. [2016] and Peres et al. [2010]. In both studies it concerned less frequent occurrence of the T allele or the TT genotype (rs2274327) in patients with high buffer capacity. The T allele was also frequently prevalent in high caries intensity; however, the differences were not statistically significant. Variant results on the same gene were obtained by Yarat et al. [2011], who linked SNP neither with the buffer capacity of saliva nor with the values of the dmft index (in the first group of patients dmft = 0, and in the second group <6).

Hereditary factors can affect the immune response of the organism. However, the vast majority of the research studies concerning this issue pertained to human leukocyte antigens, and were not SNP analyses. For this reason they were not included in the review. In this category of genes, we included studies analysing SNPs of genes encoding antimicrobial salivary peptides – *LTF* (encoding lactoferrin), *DEFB1* (encoding β-defensin 1), and *MBL* and *MASP2* (these are connected with mannose-binding protein produced in the liver, which participates in innate immune response) [Azevedo et al., 2010; Ozturk et al., 2010; Olszowski et al., 2012; Fine et al., 2013; Krasone et al., 2014; Abbasoğlu et al., 2015; Yildiz et al, 2016]. Azevedo et al. [2010] noticed the relation of allele A of lactoferrin (exon 2 *LTF*) with de-

Table 4. Overview of studies concerning genes influencing carbohydrate metabolism

Authors, year	Study population (HO/HE), *n*, age, years	Examples of examined genes: SNP/MAF	Results	Statistical approaches
Yildiz et al., 2016	HO 154 20–60	*TAS2R38*: rs713598/0.50(C)	GG genotype more frequent in low caries intensity	MA $p = 0.000$
Haznedaroğlu et al., 2015	HO 184 7–12	*TAS1R2*: rs35874116/0.27(C) rs9701796/0.20(G) *TAS1R3*: rs307355/0.24(T)	Higher caries intensity in TT homozygotes	UA, MA $p = 0.008$ $p = 0.04$
Robino et al., 2015	HO 647 44.9±12.4	*TAS1R2*: rs3935570/0.25(T) *GLUT2*: rs1499821/0.14(T)	GG genotype more frequent in high caries intensity	MA $p = 0.0117$ $p = 0.0273$
Wendell et al., 2010	HO 2,449 1–42	*TASR38*: rs713598/0.50(C) rs1726866/0.43(A) rs10246939/0.48(T) *TAS1R2*: rs4920566/0.44(A) rs9701796/0.20(G) *GNAT3*: rs2074674/0.47(A) rs6962693/0.27(G)	rs9701796 allele C connected with both high and low caries risk	UA $p = 0.02$ $p = 0.03$
Fushan et al., 2009	HE 144 No data	*TAS2R38*: rs307355/0.24(T) rs35744813/0.28(T)	Allele T connected with lower AUC saccharose index	UA Not significant $p > 0.05$

HO, homogeneous; HE, heterogeneous; UA, univariate analysis; MA, multivariate analysis; MAF, minor allele frequency.

creased caries intensity, as well as with increased salivary flow, which indicates its protective activity. A connection of a variant of the *LTF* gene with decreased caries susceptibility was observed also by Abbasoğlu et al. [2015], who defined the CT genotype as a protective factor for early childhood caries. Interesting results were also obtained by Fine et al. [2013], who observed an *LTF* gene variant that is connected with the activity of lactoferrin in saliva, which contributes to better antimicrobial response. It results in lower caries intensity in patients carrying this variant. On the other hand, Brancher et al. [2011] did not observe any SNP in the examined promoter region of the *LTF* gene in 687 twelve-year-olds of Caucasian origin.

The reception of sweet taste is stimulated by heterodimeric G proteins, encoded in *TAS1R2* and *TAS1R3* genes, and the bitter taste feeling is connected with the *TAS2R38* gene. These influence dietary habits as they cause sensitiveness or insensitiveness to some tastes [Opal et al., 2015]. Genetically conditioned sensitiveness to bitter or sweet taste may be connected with dietary preferences (cariogenic/non-cariogenic). An example can be sensitiveness/insensitiveness to PTC (phenylthiocarbamide) or PROP (propylthiouracil). Patients who are oversensitive may feel bitter or sweet taste more intensely, therefore they need a lower concentration of a substrate and, consequently, are less susceptible to caries [Darshana et al., 2014]. SNP of genes influencing taste reception, and thus carbohydrate metabolism, is a genetic factor in the aetiology of dental caries [Fushan et al., 2009; Wendell et al., 2010; Haznedaroğlu et al., 2015; Robino et al., 2015; Yildiz et al., 2016]. Hereditary fructose intolerance can

Table 5. The assessment of quality of the included studies using the Newcastle-Ottawa Scale

Authors, year	Selection	Comparability	Exposure	Total
Morrison et al., 2016	****	*	**	7
Yildiz et al., 2016	****	*	**	7
Abbasoğlu et al., 2015	****	**	**	8
Anjomshoaa et al., 2015	****	**	**	8
Haznedaroğlu et al., 2015	**	*	**	5
Robino et al., 2015	**	**	**	6
Shaffer et al., 2015	**	**	**	6
Chaussain al., 2014	****	**	**	8
Duverger et al., 2014	**	*	**	5
Krasone et al., 2014	***	*	**	6
Li et al., 2014	****	*	**	7
Fine et al., 2013	**	**	**	6
Gasse et al., 2013	****	*	**	7
Buczkowska-Radlińska et al., 2012	**	*	**	5
Koç Öztürk et al., 2012	***	*	**	6
Olszowski et al., 2012	**	*	**	5
Shimizu et al., 2012	****	**	**	8
Tannure et al., 2012b	**	**	**	6
Tannure et al., 2012a	**	**	**	6
Wang et al., 2012b	****	**	**	8
Kang et al., 2011	****	**	**	8
Yarat et al., 2011	***	**	**	7
Azevedo et al., 2010	***	*	**	6
Ozturk et al., 2010	****	**	**	8
Peres et al., 2010	***	**	**	7
Wendell et al., 2010	****	*	**	7
Fushan et al., 2009	*	*	**	4
Deeley et al., 2008	***	*	**	6
Patir et al., 2008	****	**	**	8
Slayton et al., 2005	****	**	**	8

lead to a variety of unpleasant symptoms, which occur in patients after its consumption. Therefore, they often intentionally avoid sweet food and, subsequently, have low caries intensity [Shuler, 2001].

Interesting research was presented by Weber et al. [2014]; however, it was not included in the review because of a different type of gene analysed. They examined the *ESRRB* gene for the oestrogen-related receptor-β, the mutation of which can lead to hearing impairment. The authors observed that locus 14q24.3 (*ESRRB*) can also be connected with high caries intensity in humans. Patients from different ethnic groups (n = 1,731) were examined for 25 SNPs of the *ESRRB* gene. Few SNPs were connected with caries prevalence in a Filipino population. In 2 families, 1 Turkish and the other Czech, increased caries intensity was noticed in individuals with recessive gene mutation. It was also noticed that SNP in the *ESRRB* gene (rs4903419, rs6574293) leads to weakened enamel formation, which is more prone to bacterial acid dissolution, initiating the carious process.

On the basis of the literature it can be concluded that SNPs play an important role in the aetiology of caries. Some genes (*AMELX, AQP5*, and *ESRRB*) have been checked in multiple replication studies by many independent researchers and provide a solid source of information for being the causal variant of the disease. The majority of the studied SNPs were in Hardy-Weinberg equilibrium. However, several published studies included in the present review reported so-called "suggestive" loci (p = 5e–8) with some level of biological plausibility for caries. Considering the number of hypothesis tested and the lack of replication studies, such suggestive signals could potentially be false positive, which could be a limitation of the review. Also, there is the issue of cases and controls in

the presented studies, for whom there is a doubt that they were always perfectly matched. The caries-free or caries-affected group qualification and the age of the patients should also be taken into consideration. In addition, cohort and case-control studies linking a particular gene to dental caries are too few, and these studies often neglect the role of environmental factors in dental caries development that could interact with genetic factors to induce disease. The authors emphasize that some additional studies should be performed to confirm previously obtained results in different populations, dentition types, or tooth surfaces [Zeng et al., 2013, 2014; Opal et al., 2015]. The contribution of epigenetic or environmental factors should also not be forgotten. Genetic mechanisms that modulate tooth tissue development, immune response, saliva functions, or carbohydrate metabolism are influenced by diet, hygiene, and other environmental factors. Although they all coexist in caries aetiology, the research studies usually focus on one of these components. Only a small number of studies was dedicated to analysing the interactions of genetic and environmental factors [Wang et al., 2012b; Chaussain et al., 2014; Abbasoğlu et al., 2015; Shaffer et al., 2015; Yildiz et al., 2016]. Future studies should associate some further information, such as metagenomics, protein-protein interaction, and gene expression, as they may be linked with caries [Vieira et al., 2014; Nibali et al., 2016]. Meticulous identification of every risk factor and exactly defining their mutual relations can lead to a better understanding of the character of caries in patients and hence, better prevention.

Disclosure Statement

The authors have no conflicts of interest and no financial relationships relevant to this paper to disclose.

Author Contributions

P. Piekoszewska-Ziętek conceptualized and designed the study, collected and synthesized the data, drafted the manuscript, reviewed the manuscript for important intellectual content, and approved the final manuscript as submitted. Dr. A. Turska-Szybka conceptualized the study, supervised data collection, drafted the manuscript, critically reviewed and revised the manuscript for important intellectual content, and approved the final manuscript as submitted. Prof. D. Olczak-Kowalczyk conceptualized and designed the study, coordinated and supervised data collection, drafted the manuscript, critically reviewed and revised the manuscript for important intellectual content, and approved the final manuscript as submitted.

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