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Original Article

Polymorphisms in *ENAM*, *AMBN*, and *KLK4* predispose Egyptian adults to dental caries: A cross-sectional study

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ABSTRACT

Objective: This study investigates the distributional discrepancies of four single-nucleotide polymorphic loci as correlatives and causatives of dental caries susceptibility among Egyptians.
Method: We conducted a cross-sectional study through the genotyping of enamelin (*ENAM* rs3796703), ameloblastin (*AMBN* rs4694075), tuftelin 1 (*TUFT1* rs78802584), and kallikrein 4 (*KLK4* rs2242670) in 132 adults (males = 74, females = 58) and 72 controls (males = 40, females = 32) referred from various Egyptian hospitals. For each participant, the number of decayed, missing, and filled teeth was charted, and the presence of biofilm/gingivitis/fluorosis was assessed. Bitewing radiographs were taken to detect interproximal caries. In addition, statistical analysis was conducted using Chi-square test, odds ratios, and corresponding *P*-values.
Results: The alleles and genotypes of *ENAM* rs3796703, *AMBN* rs4694075, and *KLK4* rs2242670 correlated strongly with dental caries susceptibility. However, *TUFT1* rs78802584 did not exhibit such associations.
Conclusion: These findings suggest the potential role of *ENAM*, *AMBN*, and *KLK4* as determinants of dental caries susceptibility among Egyptian adults. The role of *ENAM*, *AMBN*, and *KLK4* genetic variants is determinant in influencing susceptibility to dental caries in the Egyptian population, providing valuable insights into the genetic aspects of oral health. However, the lack of associations of caries susceptibility with *TUFT1* rs78802584 contradicts its cariogenic role in many ethnicities.

1. Introduction

In relation to tooth decay, single-nucleotide polymorphisms (SNPs) in genes that affect tooth morphology or host immunity have been studied (Chisini et al., 2018, 2020, 2021). We studied polymorphisms in enamelin (*ENAM* rs3796703), ameloblastin (*AMBN* rs4694075), tuftelin 1 (*TUFT1* rs78802584), and kallikrein 4 (*KLK4* rs2242670) encoding proteins. *ENAM* plays a role in enamel matrix formation, while *AMBN* is involved in enamel matrix assembly. Both need adequate processing to form a robust enamel layer (Jeremias et al., 2013). Furthermore, association has been confirmed between caries progression and the SNPs rs34538475 of the *AMBN* gene (Sharifi et al., 2021). Tuftelins might participate in enamel mineralization processes or act as crystal growth inhibitors, potentially contributing to enamel protection (Bayram et al., 2015). *KLK4* is an enzyme that cleaves enamel matrix proteins. It facilitates adequate enamel development by regulating enzymatic activity fundamental in protein processing (Gachova et al., 2022).

Variations in the *ENAM* gene, illustrated explicitly by SNPs such as rs3796704, rs12640848, and rs7671281, have been associated with dental caries susceptibility (Sharifi et al., 2021). These genetic differences alter the *ENAM* protein's structure and function, impacting enamel mineralization and arrangement (Moya et al., 2021; Zanolli et al., 2017). *AMBN*'s genetic mutation, especially rs34538475, corresponds to amelogenesis imperfecta. Moreover, observations on cariogenicity associated with rs4694075 SNP are inconsistent among ethnicities. Populations from Brazil, the Philippines, Turkey, and Argentina showed remarkable involvement of the C allele of rs4694075 as a potential risk allele in caries susceptibility across age ranges from toddlers (2–5 years) to older age groups (up to 72 years). The rs4970957A/G in *TUFT1* contributed to the development of caries. Furthermore, the G allele of rs4970957 has been linked to an increased susceptibility to caries development (Ergöz et al., 2014; Küchler et al.,

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2018; Sharifi et al., 2021).

This cross-sectional study aims to investigate the distributional differences of polymorphic loci, specifically *ENAM* rs3796703, *AMBN* rs4694075, *TUFT1* rs78802584, and *KLK4* rs2242670 among the Egyptian population.

2. Methods

2.1. Participants

After obtaining ethical approval (RECO6U/24–2022) on the study protocol and the suggested consent form, this study, conducted at the outpatient clinics of our University Teaching Hospital. The study followed the principles of Declaration of Helsinki and was registered in ClincalTrials.gov. It involved 132 young adults aged 15 to 22 years (males = 74, females = 58) as experimental group (Caries-susceptible group) and control of 72 individuals (40 males, 32 females) in the control group (Caries-resistant group) who were caries-free. They all presented to the Department of Operative Dentistry, Faculty of Dentistry, Outpatient Clinics of Our University Hospital, referred from various Egyptian hospitals in Greater Cairo. The intervention involved genotyping of specific genes, *ENAM* rs3796703, *AMBN* rs4694075), *TUFT1* rs78802584, and *KLK4* rs2242670. This cross-sectional study compared also dental covariates such as the number of DMF-T index, presence of biofilm, gingivitis, fluorosis, and detection of interproximal caries with caries progression. The study spanned 12 months, from November 2022 to November 2023. G-*power* software (Kang, 2021) was used to assess effective sample size (85 %). A total of 220 participants were recruited and initially enrolled in the study of whom 16 patients did not continue after 6 months.

2.2. Dental examination

Dental examinations followed the ICDAS-II. The DMF-T index assessed dental status, with patients having higher scores (>5) potentially requiring more extensive restorative interventions, while those with lower scores (up to 5) may have necessitated preventive measures to maintain oral health, unlike the control group (no caries). Gingivitis indicated poor hygiene and the potential progression to periodontal disease. Assessment of dietary habits, particularly the consumption of sugary or acidic foods and beverages, assisted in evaluating risk factors for caries development. Additionally, evaluation of oral hygiene practices, such as brushing frequency, flossing, and use of fluoride products was charted. Furthermore, tooth sensitivity, pain, or discomfort, and similar anomalies were recorded. Inter-examiner reliability assessment and the matched control group (caries-resistant group). The presence of white spots or fluorosis, indicating enamel defects or demineralization, required exclusion from the study.

Three dentists conducted visual inspections of the teeth to detect indications of decay, such as discoloration, cavities, or visible enamel softening. They employed dental probes to assess the texture and firmness of tooth surfaces, identifying softened or demineralized areas suggestive of potential caries. Radiographic imaging assessed caries severity. Bitewing radiographs detected interproximal caries that was challenging to identify through clinical examination alone.

2.3. Gene selection and justification

Epigenetic factors like DNA methylation and histone modification are known to regulate genes involved in enamel formation differently among ethnicities and age groups. The NCBI's geo and gene libraries were consulted to select SNPs. Through bootstrapping with automated backward selection, we systematically identified all relevant genetic mutations associated with susceptibility to caries. To further explore potential interactions between known genetic polymorphisms and predicted proteins, a clustered network analysis was performed using Cytoscape software and MCODE plugin. Interactions were retrieved at a confidence score threshold of 0.4 or higher.

2.4. DNA collation and genotyping

DNA collection utilized buccal swabs and maintained anonymity by using unique codes instead of personal information. DNA purification and storage were conducted per protocol, ensuring proper handling, following a recently reported protocol (Negm, 2023). The study conducted genotyping through PCR and sequencing for various SNPs. DNA was collected from all participants using buccal swabs provided in the Sigma® Cheek Cell Collection Kit in this study. These swabs were gently rubbed on both sides of the buccal mucosa ten times. After removing the plastic sticks from the swabs, the collected swabs were placed in 1.5-ml Eppendorf tubes. These tubes were then stored at + 4 °C until genomic DNA extraction. Following a brief centrifugation, DNA purification was performed following the manufacturer's instructions. The purified DNA samples were subsequently stored at −21 °C for future analysis.

Unique identification codes were assigned to the samples, maintaining anonymity by avoiding using personal identifying information like names. Researchers conducting the sample analysis and interpretation were unaware of the subjects' personal details and clinical characteristics. The identification codes were used to label the samples and all associated data. The study adhered to STROBE guidelines for observational studies, aiming to enhance research quality and transparency. Statistical analysis was conducted using SPSS (Statistical Package for Social Sciences) 29.0 software (IBM, Chicago) to calculate Chi-square test, odds ratios, and their corresponding *P* values.

3. Results

In the studied cases, 47.2 % had biofilm present, and 52.8 % had no biofilm deposits. Mild gingivitis was observed in 34 % of the cases compared to moderate and severe gingivitis, seen in 55 % and 11 % of the cases, respectively. Extensive gingivitis was significantly associated with higher odds of developing caries compared to those without gingivitis (odds ratio [OR] = 5.427, $P < .001$). Regarding sugar intake, 46.3 % of the cases reported consuming sugar up to three times, while the others reported consuming sugar more than three times daily. Nevertheless, sugar intake did not show a significant association with developing dental caries when regular brushing was maintained ($P = 0.321$).

Our in silico study identified 22 remarkable alterations in SNPs among adults. Polymorphisms in genes associated with dental enamel formation and mineralization, such as *ENAM*, *AMBN*, *TUFT1*, *MMP20*, *MMP13*, *BMP2*, *BMP4*, *PROM1*, and *TFIP11*, weakened enamel structure, development, and mineralization. Additionally, variations in genes regulating salivary composition and function, including *MUC1* and *LYZ*, affected oral microbial ecology and antimicrobial activity. *IL6* and *MBL2* polymorphisms impacted periodontal health and innate immune defense mechanisms. *KLK4* and *MAD7*, as well as those involved in cell cycle regulation and apoptosis, such as *CDKN1A*, affected proper enamel matrix processing, tissue remodeling processes, and oral tissue homeostasis. *DYM*, *ABCG2*, and *LIN7A* could have indirect roles in dental caries susceptibility. The genetic network analysis is shown in Fig. 1.

In particular, the analysis of the *ENAM* rs3796703 polymorphism revealed that allele frequencies of C and T were approximately 40.15 % and 26.52 %, respectively, in the caries-susceptible group, while the caries-resistant group displayed frequencies of 37.5 % (allele C) and 26.39 % (allele T). The chi-squared test (χ^2) showed a statistically significant association ($\chi^2 = 4.804$, $P = .036$) for allele C, indicating a potential susceptibility to dental caries (OR = 0.421, 95 % CI: 1.295–2.645).

For the *AMBN* rs4694075 variant, the allele frequencies for C and T were approximately 23.61 % and 25.76 % in the caries-susceptible group and 33.33 % and 23.61 % in the caries-resistant group,

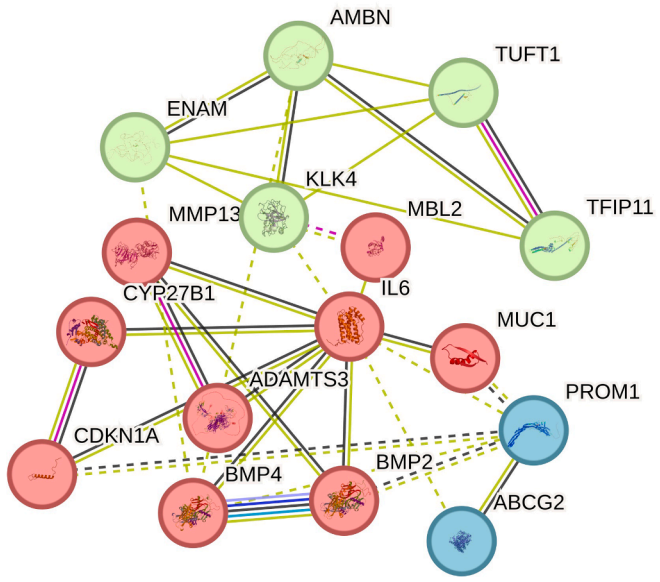

Fig. 1. Genetic network analysis for frequently detected SNPs in caries research.

respectively. The association analysis revealed a significant association of allele C with dental caries susceptibility ($\chi^2 = 2.476$, $P = .058$, OR = 0.445, 95 % CI: 0.205–0.565). Moreover, the genotype CT was significantly associated ($\chi^2 = 2.934$, $P = .037$) with dental caries susceptibility (OR = 0.061, 95 % CI: 0.255–0.975).

In the *TUFT1* gene, the A/G and A/T allele frequencies were 41.67 % and 24.42 % in the caries-susceptible group and 40.76 % and 25.17 % in the caries-resistant group, respectively. However, no statistically significant association was observed between alleles or genotypes and dental caries susceptibility.

The *KLK4* rs2242670 polymorphism displayed allele frequencies of 40.20 % (allele A/G) and 26.47 % (allele A/T) in the caries-susceptible group, and 47.06 % (allele A/G) and 21.57 % (allele A/T) in the caries-resistant group. The genotype A/G exhibited a significant association ($\chi^2 = 1.204$, $P = .007$) with dental caries susceptibility (OR = 0.301, 95 % CI: 1.135–1.895).

Overall, *ENAM* rs3796703, *AMBN* rs4694075, and *KLK4* rs2242670 gene polymorphisms were associated with dental caries susceptibility, while *TUFT1* rs78802584 showed no significant associations (Table 1).

4. Discussion

Genome-wide association studies have been instrumental in pinpointing genetic variations linked to caries susceptibility. These investigations have deepened our understanding of the genetic components influencing caries (A. Sharma et al., 2023). Caries experience was determined primarily using DMF-T scores, with adjustments for subject age to address DMF-T score limitations. Further research is warranted, including the prioritization of specific genetic regions, refining of phenotype definitions, and exploration of how genetic variants within gene sets interact.

Similar to how *ENAM* rs3796703 and *AMBN* rs4694075 gene polymorphisms were found to be deterministic in several populations (Li et al., 2021), the results were conflicting regarding the cariogenicity of *KLK4* (Biloklytska et al., 2020; Gachova et al., 2022; Sanhueza et al., 2021). Our analysis of *ENAM* rs3796703 showed notable allele frequencies of C and T in both the caries-susceptible and caries-resistant groups. A significant association was found for allele C, indicating a potential link to dental caries susceptibility.

The *AMBN* defect was linked to amelogenetic disorders, xerostomia, and caries progression in healthy and diabetic patients (Ergöz et al., 2014; Jeremias et al., 2013; Sharifi et al., 2021; Yeh et al., 2012). Our genotyping of *AMBN* rs4694075 found significant associations between allele C and genotype CT and dental caries susceptibility in the experimental group.

The *KLK4* gene, positioned at 19q13.41, is used to explore its potential link to the low incidence of cavities in primary teeth compared to the high incidence and absence of cavities in primary teeth (Weber et al., 2018). Additionally, this cross-sectional investigation analyzed two variants, *KLK4*/rs2235091 and *KLK4*/rs198968, focusing on children aged 2–5 years in Turkey. The investigation involved 259 participants, categorized as 122 without cavities and 137 with cavities. It explored these *KLK4* gene variants located within the intron—one downstream

Table 1
χ^2 measures for the studied SNPs in Egyptian adults.

Gene polymorphism	Experimental Group (Caries-susceptible group) (n = 132)	Control group (Caries-resistant group) (n = 72)	χ^2	*P*	Odds ratios
ENAM rs3796703					
Allele C	53 (40.15 %)	27 (37.50 %)	4.804	0.036	0.421 (1.295–2.645)
Allele T	35 (26.52 %)	19 (26.39 %)			
Genotype CC	27 (20.45 %)	15 (20.83 %)			
Genotype CT	13 (9.85 %)	7 (9.72 %)	2.253	0.027	0.465 (0.395–0.685)
Genotype TT	4 (3.03 %)	4 (5.56 %)	0.474	0.289	0.265 (0.09–1.90)
AMBN rs4694075					
Allele C	49 (37.12 %)	24 (33.33 %)	2.376	0.058	0.445 (0.205–0.565)
Allele T	34 (25.76 %)	17 (23.61 %)			
Genotype CC	25 (18.94 %)	14 (19.44 %)			
Genotype CT	18 (13.64 %)	12 (16.67 %)	2.934	0.037	0.061 (0.255–0.975)
Genotype TT	6 (4.54 %)	5 (6.95 %)		0.451	0.427 (0.03–4.21)
TUFT1 rs78802584					
Allele A/G	55 (41.67 %)	29 (40.28 %)	0.147	0.476	0.426 (0.485–6.905)
Allele A/T	32 (24.24 %)	21 (29.17 %)			
Genotype G/A	36 (27.27 %)	17 (23.61 %)	1.506	0.071	0.300 (1.135–1.895)
Genotype A/G	9 (6.82 %)	5 (6.94 %)	0.036	0.882	0.261 (0.295–26.225)
KLK4 rs2242670					
Allele A/G	54 (40.91 %)	36 (50.00 %)	2.375	0.058	0.426 (0.485–6.905)
Allele A/T	38 (28.79 %)	16 (22.22 %)			
Genotype A/G	28 (21.21 %)	11 (15.28 %)	1.204	0.007	0.301 (1.135–1.895)
Genotype G/A	12 (9.09 %)	9 (12.50 %)	0.034	0.028	0.261 (0.295–26.225)

Abbreviations: χ^2: Chi-squared *P*: *P* value.

and the other upstream—to understand their potential impact on dental caries susceptibility in this age group and region (Abbasoğlu et al., 2015). The SNP rs198968 A/G was linked to early childhood caries, observing protective effects against it with the genotypes AG and GG. *KLK4* polymorphism in vulnerable populations disrupts the balance between proteolytic enzymes and MMP regulation, particularly *MMP13* and *MMP20*, in terms of deteriorating enamel mineralization (Molaei & Motahari, 2022; D. Sharma & Bhandary, 2023). In contrast, the C/G SNP rs198969, especially the wild-type allele G and genotype GG and the G/A rs2235091 haplotype, were prevalent in children with dental caries (D. Sharma & Bhandary, 2023).

Polymorphisms in rs2242670 A/G and rs2978642 A/T were linked to dental caries in permanent dentition. Additionally, the A allele was linked to dental caries in rs2978642.

Finally, *TUFT1* involvement in deteriorating the microhardness of enamel in all populations has been strongly suggested (Gachova et al., 2022; Hu et al., 2019). Nonetheless, our investigation did not reveal statistically significant associations between *TUFT1* rs78802584 alleles or genotypes and dental caries susceptibility within this population. Thus, polymorphism studies should focus on the abnormal regulation of enamel structures that could be facilitated genetically and environmentally to prevent caries development among young adults (Chisini et al., 2020; Chisini, Santos, et al., 2023; Chisini, Varella de Carvalho, et al., 2023; Piekoszewska-Ziętek et al., 2017).

5. Conclusions

Polymorphism in *ENAM* rs3796703, *AMBN* rs4694075, and *KLK4* rs2242670 gene variations was associated with increased dental caries susceptibility within the Egyptian young adults. While *ENAM* rs3796703 and *AMBN* rs4694075 variants displayed consistent trends across diverse populations, conflicting outcomes were observed concerning the cariogenicity of *KLK4*. There were no significant associations between *TUFT1* rs78802584 and dental caries susceptibility. Future research endeavors may delve deeper into fathoming underlying odontogenesis and enamel regulations across different populations and age groups. Limitations of this study includes inability to exclude environmental confounders and external validity factors.

6. Institutional review board

The study was approved by Scientific Research Follow-Up Committee (SRFCO6U) and Research ethics Committee (RECO6U) at the Faculty of Dentistry, October 6 University, Giza, Egypt, with approval number: RECO6U/24-2022 obtained in its meeting held on September 12, 2022.

CRediT authorship contribution statement

Hassan Mossad Hassan Negm: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing, Visualization. **Amina Fouad Farag:** Validation, Formal analysis, Investigation, Writing – review & editing, Visualization, Supervision. **Rania Rashad Omar Omar Taha:** Validation, Formal analysis, Investigation, Resources, Data curation, Writing – review & editing, Visualization, Supervision, Project administration.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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