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Original Research Article

Association of NAT2 341C/T Gene Polymorphism and Risk of Periodontitis in Smokers: A Case-control Study

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Abstract

Background: Periodontitis, an inflammatory disease, is caused by oral biofilm, and several risk factors propagate it. Smoking is a significant risk factor that increases the severity of the disease. Arylamine *N*-acetyltransferase 2 (NAT2) enzyme present in the liver detoxify the smoke contents and renders it non-toxic to the tissues. The gene polymorphism of the NAT2 enzyme has been associated with various inflammatory diseases, including cancer.
Objectives: The current study aimed to investigate the association between NAT2 gene polymorphism at loci 341C/T in smokers with periodontitis in the ethnic Tamil population of South India.
Materials and Methods: The study had three groups, comprising smokers with healthy periodontium as the control group, smokers with periodontitis as the test group 1, and non-smokers with periodontitis as the test group 2. A total of 150 subjects were recruited, with 50 participants in each group. Periodontal parameters like clinical attachment loss (CAL), probing pocket depth (PPD), plaque index (PII), and modified sulcus bleeding index (mSBI) were evaluated. Blood samples from the participants were collected and subjected to deoxyribonucleic acid (DNA) extraction, polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assay to evaluate NAT2 gene polymorphism at the 341C/T site.
Results: The distribution of heterozygous genotype CT was slightly higher in the periodontitis group comprising smokers (62%) compared to other study groups. However, it was not statistically significant. The test groups 1 and 2 demonstrated an odds ratio of around 1.78 and 1.6, respectively, for the heterozygous genotype.
Conclusion: It can be concluded from the study that NAT2 gene polymorphism at the 341C/T site was not associated with periodontitis, irrespective of the smoking habit in the ethnic Tamil South Indian population.

Keywords

Arylamine *N*-acetyltransferase, gene polymorphism, periodontitis, smoking

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Introduction

Smoking is one of the salient environmental risk factors for periodontitis, an immunoinflammatory disease.[1] The disease is also remarkably dysregulated by genetic factors, which affect its occurrence and course.[2,3] The interrelationship of environmental and genetic factors in the field of periodontics has not been explored greatly. These factors could act synergistically in predisposing individuals to periodontitis.[4] *N*-acetyltransferase 2 (NAT2) is a phase 2 enzyme expressed in the liver, and its main function is to acetylate the smoke contents. Acetylation of smoke constituents is crucial for the detoxification of heterocyclic and aromatic amines found in the smoke. The NAT2 gene, situated on the short arm of chromosome 8, encodes the NAT2 enzyme.[5] NAT2 gene possesses highly variable sites and is comprised of a single intronless exon of 870 base pairs and encodes 290 amino acids.[6] Individuals are characterized as

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fast, intermediate, or slow acetylators based on the acetylation capacity of NAT2 enzyme.[7]

In the coding region of the NAT2 gene, there are some common sites that mark for single-nucleotide polymorphism, and they are 282C/T, 341T/C, 481C/T, 590G/A, 803A/G, and 857G/A.[8] Based on scientific literature, NAT2 gene polymorphism is positively associated with different forms of cancer and inflammatory diseases like diabetes and inflammatory bowel disease.[9–11] Therefore, it can be hypothesized that this polymorphism can pose a potential risk factor for the inflammatory disease, periodontitis. Although there are a small number of studies performed in the Caucasian population that investigated the relationship between NAT2 gene polymorphism and periodontitis, the results were inconsistent, necessitating the need for additional studies in diverse populations.[12,13] Slow acetylator genotypes were found to be predominant among the ethnic populations of South India at around 74%.[14] Nevertheless, in most of the research, smokers with the given polymorphism were more affected by cancer and other diseases than non-smokers. This gives an insight into the importance of gene-environment interactions in the development of inflammatory diseases like periodontitis. The combined effect of genetic factors and environmental exposures might result in a much higher risk of severe periodontitis than either factor alone. On that account, it is better to include smokers while studying the effects of the NAT2 gene polymorphism on periodontitis.

The 341 C/T SNP in the NAT2 gene is a well-characterized variant that alters the profile of the protein by changing isoleucine to threonine at amino acid 114. It was known to significantly affect the enzyme's acetylation activity and has been implicated in various diseases. The site 341T/C has also been identified by biocomputational tools like sorting intolerant from tolerant (SIFT) and Polyphen 2 as one of the deleterious sites in the NAT2 gene, and hence it seemed to be relevant to assess this locus of the NAT2 gene for its association with periodontitis. The rationale of this investigation was to understand the synergistic effect of environmental and genetic factors in the predisposition of the subjects to periodontitis. Hence, the present study aims to assess the association of NAT2 SNPs at loci 341T/C in smokers with periodontitis in the ethnic Tamil population of South India.

Materials and Methods

Ethical Clearance and Patient Recruitment

The study proposal was approved by the Institutional Scientific and Ethical Review Board, and the ethical clearance number is SRMDC/IRB/2019/PhD/No.117. The study was designed as a case-control study with three study groups consisting of 150 participants. Patients who reported to the Outpatient Department of Periodontics were enrolled for the study, with 50 subjects in each group.

The control group enrolled smokers with healthy periodontium with probing sulcus depth of <3 mm without attachment loss. The test groups 1 and 2 included generalized periodontitis stages II/III patients who exhibited probing pocket depth (PPD) ≥5 mm and/or clinical attachment loss (CAL) ≥3 mm in >30% of the sites (2017 World Workshop on the classification of periodontal and peri-implant diseases and conditions). Smokers with periodontitis were categorized into test group 1, and the periodontitis patients without a smoking habit were allotted to test group 2.

Inclusion and Exclusion Criteria

Systemically healthy ethnic Tamilian male subjects in the age range of 30–65 years were considered for the study. Smokers with a history of smoking for at least more than 2-year were taken into the study. Subjects were excluded if they presented with a history of diabetes mellitus, rheumatoid arthritis, or immunodeficiency disorders to avoid confounding effects; subjects who had received periodontal therapy within the last 6 months or used anti-biotics for the past 3 months were also not included in the study.

Participant Recruitment into Study Groups

Participants who satisfied the eligibility criteria were registered for the study. The participants were informed about the nature of the study, including the genetic analysis of blood samples. An informed consent form was obtained from all the participants, and they were assigned to the respective groups.

Clinical Evaluation of the Subjects

The demographic details of the study participants were recorded, which included their ethnicity, racial background, and mother tongue. A brief medical and dental history, along with smoking status, were assessed. The PPD and CAL were measured using the periodontal probe to determine periodontal diagnosis. Modified sulcus bleeding index (mSBI) by Mombelli 1987,[15] plaque index (PlI)[16] was also evaluated. A single trained investigator was utilized to assess all the clinical parameters.

Sample Collection and Genomic Deoxyribonucleic Acid (DNA) Extraction

From each participant, 2 mL of venous blood was obtained through venepuncture, which was transferred into an ethylene-diamine-tetra-acetic acid (EDTA) coated vacutainer. The samples were stored at −80°C in a deep freeze refrigerator until processing. The isolation of DNA from peripheral leukocytes was performed using PureLink™ Genomic Mini Kit. The quantity and purity of the eluted DNA were examined with Nanodrop Plus at A260/280.

Polymerase Chain Reaction—Restriction Fragment Length Polymorphism Analysis

The samples were subjected to polymerase chain reaction–restriction fragment length polymorphism assay to analyze the 341C/T site. The primers used were Forward 5′-CCTTAA CATGCATTGTGGGCAAGC-3′ and 5′-CTGATCCTTCCC AGAAATTAATTCT-3′ as reverse. The PCR was performed in 20 µL containing 50 ng of genomic DNA, 5 pmol/µL of each primer, and PCR master mix (Takara, Shiga, Japan). PCR is carried out in a thermal cycler that includes an initial denaturation at 95°C for 5 min, followed by 39 cycles of denaturation at 95°C for 35 s, primer annealing at 64°C for 35 s, extension at 72°C for 35 s and a final extension at 72°C for 5 min. The Amplicon size of PCR was 313 bp. The amplified PCR product was checked on a 1% agarose gel by electrophoresis. The amplified NAT2 PCR product was subjected to digestion using the restriction endonuclease Dde1 (New England Biolabs, UK) at 37°C for 1 h. The digested product was electrophoresed in 2% agarose with 0.5 µg/mL ethidium bromide and photographed using a gel documentation system (Figure 1). The digested products observed were genotypes CC-313 bp, CT-313+276+37 bp, and TT-276+37 bp.

To ensure the reproducibility of the RFLP results, duplicate samples were randomly selected, with 10% of the total population re-genotyped. All duplicates demonstrated 100% concordance. Genotyping accuracy was further maintained by including both positive and negative controls for each genotype and by verifying complete enzyme digestion to prevent misinterpretation of the results.

Statistical Analysis

The statistical test ANOVA was applied to analyze the age and clinical parameters like PlI, mSBI, CAL, and PPD. The pack year for the control and test group 1 was assessed by an independent *t*-test. The chi-squared test was used to analyze the variations in the frequency of genotypes and distribution between the study groups. Similarly, the allele frequency and distribution between the control and test groups were evaluated by using the chi-squared test. The strength of association between the genotypes, alleles, and periodontitis was determined using odds ratio (OR). A p value less than .05 is considered to be statistically significant.

Results

It was found that the study groups did not demonstrate significant differences with regard to age ($p = .06$). However, the intergroup comparison of clinical parameters showed that there were significant differences between the control and the test groups ($p < .001$). It was noted that the pack year also revealed significant differences between the control group and test group 1 ($p < .001$) (Table 1).

Table 2 depicts the distribution of genotypes CC, CT, TT and C, T alleles of NAT2 341C/T site in the study groups. The frequency of the genotypes CC, CT, and TT of the control groups were 10%, 58%, and 32%, respectively, and that of test group 1 was 6%, 62%, and 32%. These values were 6%, 56%, and 38%, respectively, in test group 2. The C allele is around

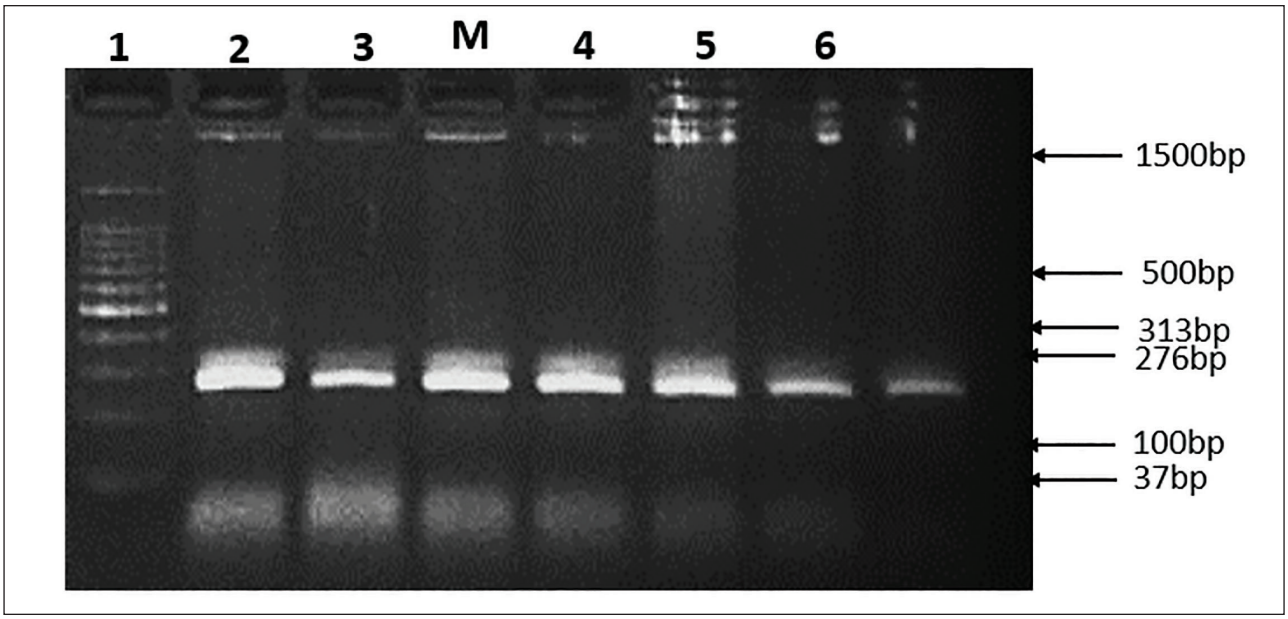


Figure 1. Agarose Gel Electrophoretogram Showing DdeI Digested Amplicon of NAT2 Gene: Homozygous: TT-276+37 bp; Heterozygous: TC-313+276+37 bp; Homozygous: CC-313 bp [Lane M = 100 bp DNA Marker].

Note: NAT2, *N*-acetyltransferase 2.

Table 1. Baseline Characteristics of the Study Groups.

Variables	Control Group (n = 50)	Test Group 1 (n = 50)	Test Group 2 (n = 50)	p Value
Age (years)	39.3 ± 9.78	43.56 ± 9.71	43.06 ± 10.07	.06
PPD (mm)	2.63 ± 0.781	6.18 ± 0.95	5.72 ± 0.67	<.001
CAL (mm)	0	3.05 ± 1.15	3.38 ± 0.49	<.001
PII	0.2 ± 0.1	2.03 ± 0.43	1.07 ± 0.06	<.001
mSBI	0.28 ± 0.17	1.8 ± 0.48	1.92 ± 0.41	<.001
Pack years	1.84 ± 1.55	3.18 ± 2.32	–	<.001

Notes: The variables were presented as mean and standard deviation. *p < .001 is highly significant. CAL, clinical attachment loss; mSBI, modified sulcular bleeding index; PII, plaque index; PPD, probing pocket depth.

Table 2. Genotype and Allele Distribution for NAT2 341C/T Polymorphism.

Genotypes	Control Group (n = 50) n (%)	Test Group 1 (n = 50) n (%)	Test Group 2 (n = 50) n (%)	Total (n = 150) n (%)	Pearson Chi-squared Test p Value
CC	5 (10)	3 (6)	3(6)	11(7.33)	χ^2 = 1.23
CT	29 (58)	31 (62)	28 (56)	88 (58.66)	p value = .87
TT	16 (32)	16 (32)	19 (38)	51 (34)	(NS)
Alleles					
C	39 (39)	37 (37)	34 (34)	110 (36.66)	χ^2 = 0.54
T	61 (61)	63 (63)	66 (66)	190 (63.33)	p value = .76 (NS)

Note: χ^2, chi-square; NS, non-significant.

Table 3. Analysis of Association and Risk Based on Genotype and Allele Distribution.

NAT2 341C/T	Test Group 1 Versus Control	Test Group 2 Versus Control
CC versus CT		
Odds ratio	1.78	1.60
95% CI (LB-UB)	0.390–8.132	0.3510–7.3773
p value	.4560	.540
CC versus TT		
Odds ratio	1.66	1.97
95% CI (LB-UB)	0.3398–8.175	0.408–9.592
p value	.529	.396
C allele versus T allele		
Odds ratio	1.08	1.24
95% CI (LB-UB)	0.6149–1.927	0.697–2.209
p value	.77	.463

Notes: p < .05—Statistically significant. CI, confidence interval; LB, lower bound; UB, upper bound.

39% in the control group and 37% and 34% in the test groups 1 and 2, respectively; whereas the T allele is 61% in the control group and around 63% and 66% in the test groups 1 and 2, respectively. The genotype and allele distribution did not show significant differences between the control and test groups.

The risk of association of the given genotypes with periodontitis was estimated using the odds ratio. The odds ratio for genotype CT in test group 1 was 1.78, with a p value of .45; for test group 2, it was 1.6, with a p value of .54; whereas for genotype TT, the odds ratio was 1.66 and 1.97 for test groups 1 and 2, respectively. The odds ratio for the allele T is 1.08 for test group 1 and 1.24 for test group 2, with a p value of .77 and .46, respectively (Table 3).

Table 4 represents Hardy–Weinberg equilibrium for genotypes. The expected numbers of the genotypes CC, CT, and TT were derived from the observed numbers. The Pearson chi-square value is 10.38, and the p value is <.001 with 1 degree of freedom.

Table 4. Hardy–Weinberg Equilibrium for Genotypes.

Genotypes	Expected	Observed
CC	20.16	11
CT	69.66	88
TT	60.16	51

Note: Pearson chi-square = 10.38; $p < .001$ with 1 degree of freedom.

Discussion

The immuno-inflammatory disease periodontitis, caused by the dysbiosis of the periodontal pathogen, is propagated by several risk factors.[17,18] The disease severity is enhanced if there is more than one risk factor, for instance, the presence of smoking and any other genetic factor associated with it.[19] In recent times, the interaction of risk factors like genetic variations and environmental factors in chronic diseases has been given marked importance.[20,21] The combined effect of genetic and environmental factors might be influential in determining the outcome of periodontal disease. NAT2 is one of the prime enzymes that function to detoxify the smoke constituents. Hence, it is relevant to evaluate the association of NAT2 gene polymorphism in periodontitis, particularly in smokers.

The NAT2 gene polymorphism at loci 341T/C has been assessed in the study, which included periodontitis patients with and without smoking habits. This study was performed to better comprehend the effect of NAT2 gene polymorphism in smokers with periodontitis. Females were not considered for the study due to prevailing social stigma in the country associated with disclosing smoking habits, and this might affect the reliability of the study results.

It was found from the results that the frequency of the homozygous CC did not differ greatly between the study groups. The distribution of CC was 10% in the control group and 6% in both the test groups. Similarly, the heterozygous CT was slightly higher in test group 1, to about 62% compared to the control group (58%) and test group 2 (56%). The homozygous variant genotype TT was marginally elevated in the test group 2 to about 38% compared to the control group and the test group (32%). The distribution of variant allele T is increased in test group 2 (66%) in comparison with test group 1 (63%) and the control group (61%).

It was quite obvious from the results obtained that although the CC genotype and C allele were elevated in the control group, they did not demonstrate significant differences between the study groups. Similarly, the frequency of variant genotype CT and TT is higher in the test groups 1 and 2, respectively. However, significant differences could not be exhibited between the study groups.

There are only a few studies available that studied the association of NAT2 gene polymorphism and periodontal disease. The first-ever study that investigated the association of NAT gene polymorphism with periodontitis was done by Meisel et al. in 2000. The Caucasian population was involved, and periodontal parameters were assessed. A questionnaire was employed to assess the smoking status of the participants. It was observed that slow acetylators of the NAT2 gene polymorphism were more prone to develop periodontitis, and the smoking habit increased the risk of periodontitis.[12] This study differed from the present study in its design and did not group smokers and non-smokers. The author concluded that the extent and severity of periodontal disease were influenced by NAT2 gene polymorphism.

A cross-sectional survey by Kocher et al. investigated the link between NAT2 polymorphism and periodontal disease. One hundred and fifty-six Caucasians who were treated for periodontitis were genotyped for NAT2 polymorphism. Both smokers and non-smokers were included, and the smoking history was self-declared by the patient. The authors reported that polymorphism in the NAT2 gene was significantly associated with periodontal bone loss. The results indicated that the slow acetylator phenotype of the NAT2 gene could be linked to an increased susceptibility to periodontitis.[13]

Another study by Meisel examined the Pomeranian population for NAT2 polymorphism. It was observed that phenotypically rapid acetylators who were smokers exhibited a higher prevalence of periodontal disease than non-smokers. The study revealed that the polymorphically expressed NAT2 genes make the subjects susceptible to periodontitis, particularly if they were smokers.[22]

The above-listed studies were the only notable studies available that considered the association of NAT2 polymorphism with periodontitis. The odds ratio for the variant genotype CT and TT for both the periodontitis groups is around 1.6–1.9 in our study, which was not significant. It was observed that there was no association between NAT2 polymorphism at site 341C/T and periodontitis, even in smoking subjects. Hardy–Weinberg equilibrium analysis of the study groups suggested the distribution of genotypes to be in harmony ($\chi^2 = 10.38$, $p < .001$), which indicated the occurrence of genotype and allele frequencies to be constant from generation to generation in an infinitely large interbreeding population.[23]

The study results were not commensurate with the other studies mentioned above, which have shown a positive association of NAT2 polymorphism with periodontitis. This may be ascribed to the differences in the study design, analyzed populations, number of cigarettes smoked, and staging of periodontitis. Different populations exhibit varying allele frequencies as a result of evolutionary processes, historical migration patterns, and the influence of natural selection. In gene-environment interaction, the link between a genetic factor and a specific disease is often influenced by environmental factors like smoking, and similarly, the impact of the environment can depend on the individual's genetic makeup. The locus analyzed and the degree of environmental exposure may vary across populations, which could explain the differences or inconsistencies observed between them.

Nevertheless, there were variations in the results obtained on the influence of NAT2 polymorphism and the development of

cancers in different ethnic groups. In studies that examined the association between NAT2 genotype variants and oral cancer, contrasting findings have emerged across various ethnic populations within India. For instance, a study involving the South Indian population reported a negative association between the susceptibility to oral cancer and NAT2 genotype variants,[24] whereas in the North Indian population, NAT2 polymorphism contributed to a higher risk of oral leukoplakia and cancer.[25]

There are multitudinous scientific literatures available that assessed the relationship of NAT2 gene polymorphism with various carcinomas like head and neck cancer, esophageal cancer, bladder cancer, breast cancer, acute lymphoblastic leukemia, and so on, in different ethnic populations.[26–31] The reports suggested that the influence and association of NAT2 gene polymorphism with different types of cancer varied across different ethnicities.

Hence, the identification of underlying genes in genetically diverse populations is important to analyze complex multifactorial diseases like periodontitis.[32] India is a country with ethnically diverse populations, and there are differences in the prevalence of NAT2 alleles even between the North and South Indian populations. In our study, the Tamil ethnic South Indian population were recruited for genetic analysis. We were unable to compare our findings with other Indian ethnic groups due to the lack of association studies on NAT2 gene variations and periodontitis.

Patients need to be educated about the genetic predisposition and environmental factors, and how it has an impact on the development of various diseases. The sample size was small, which could be a limitation of the study, and larger sample sizes are preferable for association studies. Excluding females from the study limits external validity by making the findings less applicable to women. Adopting a more inclusive approach that ethically and sensitively involves female participants would enhance the external validity of the research.

Future studies should consider populations with specific ethnic diversity and consider heavy smokers to determine the gene-environment interaction appropriately in periodontal diseases. The findings of this study were preliminary and necessitate larger, well-designed case-control studies including other SNPs of the NAT 2 gene.

Conclusion

The variant genotypes CT and TT of the NAT2 gene at 341C/T were not associated with periodontitis in the study population. Given the limitations of our study, it can be concluded that the NAT2 gene polymorphism at 341C/T was not associated with periodontitis patients, even in smokers in the ethnic Tamil South Indian population.

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Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval and Informed Consent

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References

1. Apatzidou DA. The role of cigarette smoking in periodontal disease and treatment outcomes of dental implant therapy. *Periodontol 2000* 2022; 90(1): 45–61. doi: 10.1111/prd.12449
2. Schaefer AS. Genetics of periodontitis: discovery, biology, and clinical impact. *Periodontol 2000* 2018; 78(1): 162–173. doi: 10.1111/prd.12232
3. Shaddox LM, Morford LA and Nibali L. Periodontal health and disease: the contribution of genetics. *Periodontol 2000* 2021; 85(1): 161–181. doi: 10.1111/prd.12357
4. Loos BG and Van Dyke TE. The role of inflammation and genetics in periodontal disease. *Periodontol 2000* 2020; 83(1): 26–39. doi: 10.1111/prd.12297
5. Wichukchinda N, Pakdee J, Kunhapan P, et al. Haplotype-specific PCR for NAT2 diplotyping. *Hum Genome Var* 2020; 7: 13. doi: 10.1038/s41439-020-0101-7
6. Choudhury C, Gill MK, McAleese CE, et al. The arylamine *N*-acetyltransferases as therapeutic targets in metabolic diseases associated with mitochondrial dysfunction. *Pharmacol Rev* 2024; 76(2): 300–320. doi: 10.1124/pharmrev.123.000835
7. Al-Ahmad MM, Amir N, Dhanasekaran S, et al. Studies on *N*-acetyltransferase (NAT2) genotype relationships in Emiratis: confirmation of the existence of phenotype variation among slow acetylators. *Ann Hum Genet* 2017; 81(5): 190–196. doi: 10.1111/ahg.12198
8. Hein DW and Doll MA. Accuracy of various human NAT2 SNP genotyping panels to infer rapid, intermediate and slow acetylator phenotypes. *Pharmacogenomics J* 2012; 13(1): 31–41. doi: 10.2217/pgs.11.122
9. Banjoko SO and Akinlade KS. Acetylation pharmacogenetics and renal function in diabetes mellitus patients. *Indian J Clin Biochem* 2010; 25(3): 289–294. doi: 10.1007/s12291-010-0055-5
10. Baranska M, Trzcinski R, Dziki A, et al. The role of *N*-acetyltransferase 2 polymorphism in the etiopathogenesis of inflammatory bowel disease. *Dig Dis Sci* 2011; 56(7): 2073–2080. doi: 10.1007/s10620-010-1527-4

11. Walia HK, Singh N and Sharma S. Association of NAT2 gene polymorphisms toward lung cancer susceptibility and prognosis in North Indian patients treated with platinum-based chemotherapy. *Pharmacogenom J* 2022; 23(2): 97–118. doi: 10.2217/pgs-2021-0080
12. Meisel P, Timm R, Sawaf H, et al. Polymorphism of the *N*-acetyltransferase (NAT2), smoking and the potential risk of periodontal disease. *Arch Toxicol* 2000; 74(6): 343–348. doi: 10.1007/s002040000136
13. Kocher T, Sawaf H, Fanghänel J, et al. Association between bone loss in periodontal disease and polymorphism of *N*-acetyltransferase (NAT2). *J Clin Periodontol* 2002; 29(1): 21–27. doi: 10.1034/j.1600-051x.2002.290104.x
14. Anitha A and Banerjee M. Arylamine *N*-acetyltransferase 2 polymorphism in the ethnic populations of South India. *Int J Mol Med* 2003; 11(1): 125–131.
15. Newbrun E. Indices to measure gingival bleeding. *J Periodontol* 1996; 67(6): 555–561. doi: 10.1902/jop.1996.67.6.555
16. Silness J and Loe H. Periodontal disease in pregnancy. II correlation between oral hygiene and periodontal condition. *Acta Odontol Scand* 1964; 22: 121–135. doi: 10.3109/00016356408993968
17. Loka AM, Ponnaiyan D, Parthasarathy H, et al. Association of the CASP3 rs4647602 gene polymorphism with periodontitis in south Indians of Tamil ethnicity. *Genet Test Mol Biomark* 2022; 26(7–8): 391–397. doi: 10.1089/gtmb.2022.0018
18. Varadharajulu G, Victor DJ and Venkadassalapathy Sl. Expression of NLRP3 and superoxide dismutase-2 (SOD2) in the gingival tissues of periodontitis patients with and without type 2 diabetes mellitus: a case-control study. *Int J Diabetes Dev Ctries* 2023; 1–9. doi: 10.1007/s13410-023-01290-5
19. Freitag-Wolf S, Munz M, Wiehe R, et al. Smoking modifies the genetic risk for early-onset periodontitis. *J Dent Res* 2019; 98(12): 1332–1339. doi: 10.1177/0022034519875443
20. Agustí A, Melén E, DeMeo DL, et al. Pathogenesis of chronic obstructive pulmonary disease: understanding the contributions of gene-environment interactions across the lifespan. *Lancet Respir Med* 2022; 10(5): 512–524. doi: 10.1016/S2213-2600(21)00555-5
21. Wilke RA and Larson EA. Air, land, and sea: gene-environment interaction in chronic disease. *Am J Med* 2021; 134(12): 1476–1482. doi: 10.1016/j.amjmed.2021.07.006
22. Meisel P, Heins G, Carlsson L, et al. Impact of genetic polymorphisms on the smoking-related risk of periodontal disease: the population-based study SHIP. *Tob Induc Dis* 2003; 1(1): 197. doi: 10.1186/1617-9625-1-3-197
23. Crena J, Subramanian S, Victor DJ, et al. Single nucleotide polymorphism at -1087 locus of interleukin-10 gene promoter is associated with severe chronic periodontitis in nonsmoking patients. *Eur J Dent* 2015; 9(3): 387–393. doi: 10.4103/1305-7456.163237
24. Balaji L, Krishna BS and Bhaskar LV. An unlikely role for the NAT2 genotypes and haplotypes in the oral cancer of south Indians. *Arch Oral Biol* 2012; 57(5): 513–518. doi: 10.1016/j.archoralbio.2011.10.019
25. Nigam K, Gupta S, Gupta OP, et al. Alteration of the risk of preoral cancer and cancer in North Indian population by NAT1 and NAT2 polymorphisms genotypes and haplotypes. *Head Neck Surg* 2021; 278(10): 4081–4089. doi: 10.1007/s00405-021-06774-w
26. Demokan S, Suoglu Y, Gözeler M, et al. *N*-acetyltransferase 1 and 2 gene sequence variants and risk of head and neck cancer. *Mol Biol Rep* 2010; 37(7): 3217–3226. doi: 10.1007/s11033-009-9905-8
27. Matejcic M, Vogelsang M, Wang Y, et al. NAT1 and NAT2 genetic polymorphisms and environmental exposure as risk factors for oesophageal squamous cell carcinoma: a case-control study. *BMC Cancer* 2015; 15: 150. doi: 10.1186/s12885-015-1105-4
28. Teleka S, Jochems SHJ, Jirström K, et al. The interaction between smoking and bladder cancer genetic variants on urothelial cancer risk by disease aggressiveness. *Cancer Med* 2022; 11(15): 2896–2905. doi: 10.1002/cam4.4654
29. Wang T and Marei HE. Landscape of NAT2 polymorphisms among breast cancer. *Biomed Pharmacother* 2016; 77: 191–196. doi: 10.1016/j.biopha.2015.12.011
30. Zgheib NK, Shamseddine AA, Geryess E, et al. Genetic polymorphisms of CYP2E1, GST, and NAT2 enzymes are not associated with risk of breast cancer in a sample of Lebanese women. *Mutat Res* 2013; 747–748: 40–47. doi: 10.1016/j.mrfmmm.2013.04.004
31. Jiang WH, Wang XT, Zheng LD, et al. Relationship between NAT2 polymorphisms and onset risk of acute leukemia: a systematic review and meta-analysis. *Eur Rev Med Pharmacol Sci* 2019; 23(21): 9259–9266. doi: 10.26355/eurrev_201911_19418
32. Indian Genome Variation Consortium. Genetic landscape of the people of India: a canvas for disease gene exploration. *J Genet* 2008; 87(1): 3–20. doi: 10.1007/s12041-008-0002-x