**CAROL DAVILA UNIVERSITY OF MEDICINE AND PHARMACY, BUCHAREST**
**DOCTORAL SCHOOL, DENTAL MEDICINE FIELD**

# PhD THESIS SUMMARY

**PhD Supervisor:**
**PROF. ECATERINA IONESCU, MD, PhD**

**PhD Candidate:**
**ALBU ȘTEFAN-DIMITRIE**

**2024**

**CAROL DAVILA UNIVERSITY OF MEDICINE AND PHARMACY, BUCHAREST**
**DOCTORAL SCHOOL**
**DENTAL MEDICINE FIELD**

# CONSIDERATIONS ON THE GENETIC IMPLICATIONS IN PERIODONTAL AND ORTHODONTIC PATHOLOGY

**PhD THESIS SUMMARY**

**PhD Supervisor:**
**PROF. ECATERINA IONESCU, MD, PhD**

**PhD Candidate:**
**ALBU ȘTEFAN-DIMITRIE**

**2024**

**Table of Contents**

**List of Published Scientific Papers:** ........ **I**
**List of Abbreviations:** ........ **II**
**List of Tables:** ........ **IV**
**List of Figures:** ........ **IX**

**Introduction** ........ **1**

**I. GENERAL SECTION** ........ **5**

**Chapter 1** ........ **5**
**1. Periodontal Disease: Etiopathogenesis, Classification, Microbial and Immunological Implications** ........ **5**
- **1.1. Etiopathogenesis of Periodontal Disease** ........ **6**
- **1.2. Classification of Periodontal Disease** ........ **9**
- **1.3. Microbial Implications in Periodontal Disease** ........ **10**
- **1.4. Immunological Implications in Periodontal Disease** ........ **13**

**Chapter 2** ........ **16**
**2. Dento-Maxillary Anomalies: Etiopathogenesis, Classification, and Implications in Periodontal Pathology** ........ **16**
- **2.1. Etiopathogenesis of Dento-Maxillary Anomalies** ........ **16**
- **2.2. Classification of Dento-Maxillary Anomalies** ........ **18**
- **2.3. Implications of Dento-Maxillary Anomalies in Periodontal Pathology** ........ **20**

**Chapter 3** ........ **25**
**3. Considerations on the Genetic Factor's Implications in Periodontal and Orthodontic Pathology** ........ **25**
- **3.1. Genetic Factor Implications in Periodontal and Orthodontic Pathology** ........ **26**
- **3.2. Genetic Polymorphisms Implications in Orthodontic Pathology** ........ **28**
- **3.3. Genetic Polymorphisms Implications in Periodontal Pathology** ........ **29**

II. PERSONAL SCIENTIFIC RESEARCH ........................................... 32

Chapter 4 ........................................................................................ 32
4. General Methodology of Scientific Research ........................................... 32
4.1. Hypothesis, Aim, and General Objectives........................................ 32
4.2. Research Groups........................................................................... 33
4.3. Research Method ......................................................................... 34
4.4. Data Processing ........................................................................... 35

Chapter 5 ........................................................................................ 36
5. Study on the Determination of Bacterial Load in Patients with Periodontal Disease and Associated Dento-Maxillary Anomalies........................................ 36
5.1. Introduction ................................................................................ 36
5.2. Materials and Methods ................................................................. 37
5.3. Results ........................................................................................ 47
5.4. Discussions .................................................................................. 73
5.5. Conclusions ................................................................................. 79

Chapter 6 ........................................................................................ 80
6. Comparative Study on the Determination of Bacterial Load Characteristics in Patients with Periodontal Disease and Dento-Maxillary Anomalies.................... 80
6.1. Introduction ................................................................................ 80
6.2. Materials and Methods ................................................................. 81
6.3. Results ........................................................................................ 84
6.4. Discussions .................................................................................. 110
6.5. Conclusions ................................................................................. 117

Chapter 7 ........................................................................................ 119
7. Study on the Determination of the Inflammatory Genetic Profile through the Analysis of Single Nucleotide Polymorphisms in IL-1A, IL-1B, IL-1RN, IL-6, and TNF-α........................................................................................ 119
7.1. Introduction ................................................................................ 119
7.2. Materials and Methods ................................................................. 120

**7.3. Results ........................................................................ 125**
**7.4. Discussions ........................................................................ 139**
**7.5. Conclusions ........................................................................ 147**

**Chapter 8 ........................................................................ 148**
**8. Conclusions, Personal Contributions, and Future Directions for Development... 148**
**Bibliography........................................................................ 152**

# Introduction

The scientific motivation for the present research on the genetic implications in periodontal and orthodontic pathology is closely related to the significant impact of dento-maxillary anomalies on oral health. These anomalies, from the increased risk of periodontal disease to the damage of supporting tissues, bone resorption, and progression of periodontal disease, necessitate the planning of an integrated, personalized, and innovative treatment approach that positively impacts patients' quality of life.

Epidemiological studies and clinical research in the field indicate strong links between dento-maxillary abnormalities and the prevalence of periodontal disease across different population groups. This facilitates the identification of specific risk factors and the development of more effective strategies for prevention, early personalized diagnosis, and targeted treatment. These advancements are made possible through an interdisciplinary and effective approach to dento-maxillo-periodontal pathology.

The study of genetic implications in periodontal and orthodontic pathology provides strong *scientific motivation* for both dental professionals and researchers. It offers clinicians the opportunity to adopt therapeutic approaches that are not only complex but also deeply interdisciplinary, aligning with the latest scientific discoveries. Simultaneously, researchers are encouraged to explore new perspectives, further deepening the understanding of the link between dento-maxillary abnormalities and periodontal disease."

The *importance, novelty, and current relevance* of my research topic lie in the complexity of the molecular-level research strategy, which explores the intricate relationship between two key dental specialties: orthodontics and periodontics. The interdisciplinary nature of this topic is drawing increased attention from the scientific community and oral health professionals, highlighting its potential to revolutionize the understanding and management of dento-maxillary anomalies within the context of modern, holistically integrated medical practice. While dental treatments were previously limited to a singular, unidisciplinary approach, recent advances in scientific research and the adoption of modern technologies – from imaging and computer modeling to molecular genetics – now enable the identification of risk factors, the early implementation of specific preventive measures, accurate diagnosis, and appropriate treatment planning within multidisciplinary and interdisciplinary teams.

This *topic* is highly relevant, not only at the national level but also internationally, due to the very limited number of studies in the specialized literature that analyze the direct impact of molecular genetics research on periodontal pathology associated with dento-maxillary anomalies.

The *general hypothesis* underlying my scientific research is that dento-maxillary anomalies, in close correlation with microbial and immunological factors, and potentiated by the unique genetic profile of each individual, represent major risk factors associated with the development and progression of periodontal disease.

In the current era of genomics and proteomics, the specific objectives of this research go beyond the identification and quantification of bacterial load in patients with periodontal disease and dento-maxillary anomalies using advanced genomic microbiology methods. The research also aims to develop the inflammatory genomic profile of patients by analyzing single nucleotide polymorphisms (SNPs) in the most relevant genes, associated with biomolecules that have potential as inflammatory biomarkers. This approach not only enhances the understanding of the pathogenic mechanisms of periodontal disease in the context of dento-maxillary anomalies, but also advances the potential for diagnosis and personalized treatment of patients.

To achieve the proposed objectives, we utilized the most advanced *methods and techniques in genetic investigation at the molecular level*, employing state-of-the-art technology that enabled sample processing according to the highest standards of molecular genetics. Specifically, we conducted a quantitative and qualitative microbiological analysis of 12 periodontopathogenic bacterial species using the qRT-PCR (quantitative Real-Time Polymerase Chain Reaction) method with the Bio-Rad CFX-96 Real-Time system, managed through Bio-Rad CFX Maestro 2.0 software (Bio-Rad Laboratories, Inc., Hercules, CA, USA). Additionally, we analyzed single nucleotide polymorphisms (SNPs) of pro-inflammatory cytokines—IL-1A, IL-1B, IL-1RN, IL-6, and TNF-α—utilizing Fluidigm microfluidics technology (Fluidigm Corporation, South San Francisco, CA, USA).

The *scientific research methodology* was based on an interdisciplinary approach aimed at deeply investigating the impact of dento-maxillary anomalies on periodontal disease. The study integrates clinical, microbiological, and genetic dimensions, providing a holistic approach to this pathology. To ensure the validity and reliability of the data, the research was structured into three studies, conducted on two and three distinct groups of participants, respectively, selected according to strict inclusion and exclusion criteria to ensure group homogeneity and the relevance of the results. The three groups of participants

were as follows: Group 1: Patients diagnosed with both periodontal disease and dento-maxillary abnormalities; Group 2: Patients with periodontal disease but without dento-maxillary abnormalities; and Group 3: Clinically healthy subjects without periodontal disease or dento-maxillary abnormalities. This structure enabled a detailed comparative analysis between groups, facilitating the identification of significant correlations between the presence of dento-maxillary anomalies and the progression of periodontal disease in relation to microbial, immunological factors, and individual genetic predisposition.

The thesis is structured into two main sections, with a coherent framework that harmoniously combines theoretical aspects with original personal research.

The *general section* is divided into three chapters. In this context, Chapter 1, titled 'Periodontal Disease: Etiopathogenesis, Classification, Microbial and Immunological Implications,' Chapter 2, titled 'Dento-Maxillary Anomalies: Etiopathogenesis, Classification, Implications in Periodontal Pathology,' and Chapter 3, titled 'Considerations on the Genetic Factor's Implications in Periodontal and Orthodontic Pathology,' illustrate the current state of knowledge regarding genetic implications in periodontal and orthodontic pathology.

In the *second part*, dedicated to personal contributions, I have presented three original studies, each involving an in-depth investigation of the interactions between dento-maxillary anomalies and periodontal disease, in correlation with genomic microbiology and individual genetic predisposition.

The *first study*, titled 'Study on the Determination of Bacterial Load in Patients with Periodontal Disease and Associated Dento-Maxillary Anomalies,' analyzes the microbial load of 12 bacterial strains in patients with dento-maxillary anomalies and periodontal disease, compared to patients with periodontal disease but without dento-maxillary anomalies.

The *second study*, titled 'Comparative Study on the Determination of Bacterial Load Characteristics in Patients with Periodontal Disease and Dento-Maxillary Anomalies,' which is a continuation of the previous study, aims to compare the microbial load of 12 bacterial strains between patients with periodontal disease and dento-maxillary anomalies, patients with periodontal disease without dento-maxillary anomalies, and clinically healthy patients without periodontal disease or dento-maxillary anomalies.

The *third study*, titled 'Study on the Determination of the Inflammatory Genetic Profile through the Analysis of Single Nucleotide Polymorphisms in IL-1A, IL-1B, IL-1RN, IL-6, and TNF-α Interleukins,' aims to determine the genomic inflammatory profile in

periodontal and orthodontic pathology by analyzing genetic polymorphisms of pro-inflammatory markers, including IL-1A, IL-1B, IL-1RN, IL-6 interleukins, and tumor necrosis factor alpha (TNF-α) in patients with dento-maxillary anomalies and periodontal disease versus patients with periodontal disease but without dento-maxillary anomalies.

The *results* of my personal scientific research provide new insights into the specific mechanisms of action of various bacterial species that contribute to the initiation and progression of periodontal disease, highlighting the importance of personalized clinical management tailored to the microbiological and genetic characteristics of each patient. These studies underscore the need for an integrated and innovative approach to orthodontic and periodontal pathology, with the potential to significantly enhance patients' quality of life.

My research has a strong *interdisciplinary and multidisciplinary nature,* evidenced by the impact of genomic research on microbial and immunological factors in the context of the orthodontics-periodontology relationship. This approach fosters a deep and comprehensive understanding of the fundamental mechanisms of 21st-century medicine, characterized by a predictive, preventive, personalized, and participatory genomics approach.

The personal research began with a pilot study, which was progressively expanded based on the available time and financial resources. Consequently, this research presents several *limitations* that must be considered to properly understand the context and relevance of the results. The small sample size may limit the statistical power of the conclusions and reduce the applicability of the findings to a broader population. Additionally, the diversity of participants, restricted to a single geographic region, may limit the observed genetic variability. Furthermore, the analysis of a limited number of bacterial strains hinders the full understanding of the microbial factor's involvement in periodontal and orthodontic pathology. Similarly, the limited selection of individual genetic markers analyzed restricts the evaluation of other potentially relevant genetic variants in oral pathology. Recognizing these limitations is essential for guiding more comprehensive and rigorous future research, ensuring a deeper assessment of the complex relationships between bacterial species, individual genetic polymorphisms, and the progression of the studied conditions.

By implementing future research directions—such as expanding sample sizes, diversifying studied populations, analyzing a broader spectrum of bacterial strains, and investigating a greater number of mononucleotide sequences—I propose the expansion of this study within a larger research project. This project will be designed with scientific rigor

and strategic vision, carried out by a team of passionate young researchers and esteemed experts recognized for their field expertise. This transdisciplinary approach will provide new perspectives and innovative methodologies, ultimately contributing to improved medical practices and significantly enhancing patient quality of life.

# PERSONAL SCIENTIFIC RESEARCH

## General Research Methodology

The *general hypothesis* underpinning my scientific research is that dento-maxillary anomalies, potentiated by the unique genetic profile of each individual, represent major risk factors associated with the development and progression of periodontal disease.

The two *primary objectives* of my scientific research were as follows:

1. Quantitative and qualitative evaluation of periodontopathogenic bacteria using advanced molecular genetics techniques (qRT-PCR), by determining their prevalence and concentration in the studied cohorts. In the first study, the research aimed to compare the bacterial load between two cohorts of patients: those with periodontal disease (PD) and dento-maxillary anomalies (DMA) versus patients with PD but without DMA. In the second study, the research was expanded by introducing a third cohort consisting of clinically healthy patients, without PD or DMA.
2. Evaluation of the individual genomic inflammatory profile through the analysis of single nucleotide polymorphisms (SNPs) of interleukins (IL-1A, IL-1B, IL-1RN, and IL-6) and tumor necrosis factor-alpha (TNF-alpha) in patients with PD and DMA versus patients with PD without DMA, with the goal of identifying genetic variants associated with increased susceptibility to PD in the context of DMA. This study required establishing the genotype-phenotype relationship in the two patient cohorts and identifying how these polymorphisms influence the inflammatory response and progression of PD in patients with DMA.

My personal research involved the selection of a variable number of patients, grouped into three cohorts. Two studies (Study 1 and Study 3) were conducted on two cohorts of patients (*Cohort 1*: Patients with PD and DMA, *Cohort 2*: Patients with PD without DMA), while Study 2 included the analysis of three cohorts (*Cohort 1*: Patients with PD and DMA,

*Cohort 2*: Patients with PD without DMA, and *Cohort 3*: Clinically healthy patients, without PD or DMA).

Regarding *demographic information*, including age, sex, education level, and smoking habits, along with clinical and diagnostic data, these were collected and documented from patient records.

The method used in the first two studies involved quantitative and qualitative microbiological analysis of 12 bacterial strains using the real-time quantitative polymerase chain reaction (qRT-PCR) technique, with the Bio-Rad CFX-96 Real-Time system, controlled by the Bio-Rad CFX Maestro 2.0 software (Bio-Rad Laboratories, Inc., Hercules, CA, USA).

The method employed for identifying genetic polymorphisms of pro-inflammatory markers of interleukins (IL-1A, IL-1B, IL-1RN, IL-6, and TNF-α) involved genotyping the following single nucleotide polymorphisms: IL-1A rs1800587, IL-1B rs1143634, IL-1RN rs419598, IL-6 rs1800795, and TNF-α rs1800629, using Fluidigm microfluidic technology (Fluidigm Corporation, South San Francisco, California, USA).

The collected data were organized and prepared for statistical analysis, with incomplete or erroneous entries eliminated. For statistical analysis and interpretation of results, IBM SPSS Statistics 25 and Microsoft Office Excel/Word 2021 were utilized.

## Study 1: Study on the Determination of Bacterial Load in Patients with Periodontal Disease and Associated Dento-Maxillary Anomalies

### Introduction

The study aimed at determining the bacterial load of 12 periodontopathogenic bacterial species in two groups of patients and was conducted at the Faculty of Dentistry, "Carol Davila" University of Medicine and Pharmacy in Bucharest, with the approval of the Scientific Research Ethics Commission (protocol number: 27652/02.02.2024) and in accordance with the Helsinki Declaration of 1975 **[14]**.

All patients received written information regarding the details of the scientific research, accepted, and signed the "Informed Patient Consent" and "Consent regarding the protection of personal data."

The *primary objective* of the research was to compare the bacterial load of 12 periodontopathogenic species between two patient groups: Group 1, consisting of patients

with dento-maxillary anomalies (DMAn) and periodontal disease, and Group 2, consisting of patients with periodontal disease (PD) but without DMAn.

The *working hypothesis* of the study is that DMAn creates local conditions favorable for the colonization and proliferation of periodontopathogenic bacteria, leading to an increased bacterial load in patients with DMAn compared to those without DMAn.

The *specific objectives* of the study were to determine the bacterial load of *Aggregatibacter actinomycetemcomitans*, *Porphyromonas gingivalis*, *Treponema denticola*, *Tannerella forsythia*, *Eikenella corrodens*, *Campylobacter rectus*, *Prevotella intermedia*, *Fusobacterium nucleatum*, *Prevotella nigrescens*, *Capnocytophaga ochracea*, *Capnocytophaga sputigena*, and *Capnocytophaga gingivalis* in patients with PD and DMAn versus PD patients without DMAn.

## Material and Method

All participants in the study were divided into two distinct groups:

- **Group 1**: Patients with dento-maxillary anomalies and periodontal disease.
- **Group 2**: Patients with periodontal disease, but without dento-maxillary anomalies.

## Results

The *quantitative analysis* of the bacterial load of the 12 bacterial strains indicated significantly increased levels of red complex species in patients with dento-maxillary anomalies (DMAn) compared to those without DMAn. Specifically, the concentrations of *Tannerella forsythia* (p=0.020, mean = 6.04 ± 0.72 vs. mean = 4.4 ± 1.89), *Treponema denticola* (p=0.023, median = 4.32, IQR = 2.76-5.53 vs. median = 1.93, IQR = 0-3.19), and *Porphyromonas gingivalis* (p=0.002, median = 5.64, IQR = 4.94-5.98 vs. median = 2.48, IQR = 0-4.05) were significantly higher in patients with DMAn **[14]**.

In the study of bacteria with a moderate degree of pathogenicity, among the orange complex bacteria, only *Eikenella corrodens* (p=0.040, mean = 4.55 ± 1.02 vs. mean = 3.23 ± 1.56), *Campylobacter rectus* (p<0.001, mean = 4.2 ± 0.56 vs. median = 1.8 ± 1.51), and *Prevotella intermedia* (p=0.043, median = 5.04, IQR = 0-5.49 vs. median = 0, IQR = 0-3.39) were significantly elevated in patients with DMAn compared to those without DMAn **[14]**. Conversely, *Fusobacterium nucleatum* and *Prevotella nigrescens* were significantly increased in patients without DMAn **[14]**.

In the analysis of bacteria with a low degree of pathogenicity, among the green complex bacteria, only *Capnocytophaga sputigena* (p=0.011, median = 5.91, IQR = 5.47-

6.17 vs. median = 4.63, IQR = 3.83-5.64) and *Capnocytophaga gingivalis* (p=0.007, median = 5.87, IQR = 5.34-6.03 vs. median = 4.4, IQR = 3.5-5.71) were significantly elevated in patients with DMAn compared to those without DMAn **[14]**.

In the *qualitative analysis* of the 12 microbial strains with varying degrees of periodontal pathogenicity (high, medium, and low), each bacterium was evaluated based on its presence in the two patient groups. The study showed that *Porphyromonas gingivalis* was significantly more frequently associated with DMAn, being present in 90% of patients, compared to 30% of patients without DMAn (p=0.028). Conversely, *Treponema denticola* (p=0.106) and *Tannerella forsythia* (p=0.474) did not show significant differences between the two groups.

Regarding *Aggregatibacter actinomycetemcomitans* (p=0.517), a bacterium with a high degree of periodontopathogenicity, no significant differences were observed between the two groups, indicating that its concentration was not significantly different between patients with or without DMAn.

The qualitative analysis of bacteria with a moderate degree of pathogenicity indicated that for the orange complex bacteria, *Eikenella corrodens* (p=1.000), *Campylobacter rectus* (p=0.474), *Prevotella intermedia* (p=0.073), *Fusobacterium nucleatum* (p=0.325), and *Prevotella nigrescens* (p=1.000), the differences between the groups were not statistically significant based on the Fisher test. Therefore, the concentration levels of these bacteria were not significantly different between patients with or without DMAn.

The qualitative analysis of bacteria with a low degree of pathogenicity revealed that, among the green complex bacteria, *Capnocytophaga sputigena* was present in 50% of patients with PD and DMAn, compared to 0% of patients with PD but without DMAn (p=0.033). In contrast, *Capnocytophaga ochracea* (p=1.000) and *Capnocytophaga gingivalis* (p=0.474) did not show significant differences between the two groups, indicating that their concentration levels were not significantly different between patients with and without DMAn.

## Conclusions

1. The study demonstrates a significant correlation between the presence of dento-maxillary anomalies (DMAn) and an increased load of periodontopathogenic bacteria, particularly from the red and orange microbial complexes.

2. Periodontal pathogens with high pathogenicity, including *Treponema denticola*, *Tannerella forsythia*, and *Porphyromonas gingivalis*, were observed in significantly higher concentrations in patients with DMAn compared to those without DMAn.
3. Moderately periodontogenic bacteria, such as *Eikenella corrodens*, *Campylobacter rectus*, and *Prevotella intermedia*, were also present in significantly higher concentrations in DMAn patients.
4. Periodontopathogenic bacteria of lower pathogenicity, including *Capnocytophaga sputigena* and *Capnocytophaga gingivalis*, were detected in significantly higher concentrations in DMAn patients.
5. *Aggregatibacter actinomycetemcomitans*, *Fusobacterium nucleatum*, and *Prevotella nigrescens* were detected in significantly higher concentrations in patients without DMAn.
6. The bacterial load of *Capnocytophaga ochracea* did not differ significantly between patients with and without dento-maxillary abnormalities.
7. Patients with elevated concentrations of *Porphyromonas gingivalis* and *Capnocytophaga sputigena* were significantly more frequently associated with the presence of dento-maxillary abnormalities.

## Study 2: Comparative Study on the Determination of Bacterial Load Characteristics in Patients with Periodontal Disease and Dento-Maxillary Anomalies

### Introduction

This study continues previous research, aiming to compare the bacterial load between the following groups of subjects: patients with periodontal disease associated with dento-maxillary anomalies, patients with periodontal disease without dento-maxillary anomalies, and clinically healthy individuals.

The specific objectives focused on comparing the bacterial load of 12 periodontopathogenic bacterial species belonging to the violet complex (*Aggregatibacter actinomycetemcomitans*), the red complex (*Porphyromonas gingivalis*, *Treponema denticola*, and *Tannerella forsythia*), the orange complex (*Eikenella corrodens*, *Campylobacter rectus*, *Prevotella intermedia*, *Fusobacterium nucleatum*, and *Prevotella nigrescens*), and the green complex (*Eikenella corrodens*, *Campylobacter rectus*, *Prevotella*

*intermedia*, *Fusobacterium nucleatum*, and *Prevotella nigrescens*) in patients with periodontal disease (PD) and dento-maxillary anomalies (DMA), compared to those with PD only, without DMA, as well as to clinically healthy patients without PD or DMA.

**Material and Method**

All participants in the study were divided into three distinct groups:

- Group 1: Patients with dento-maxillary anomalies (DMAn) and periodontal disease.
- Group 2: Patients with periodontal disease (PD), but without dento-maxillary anomalies.
- Group 3: Patients without dento-maxillary anomalies or periodontal disease.

For Groups 1 and 2, the inclusion and exclusion criteria are identical to those presented in the previous study. Therefore, I will focus on the specific characteristics of the third group.

**Results**

The quantitative analysis of highly pathogenic bacteria indicated that *Tannerella forsythia* (p=0.007) and *Porphyromonas gingivalis* (p=0.002) showed statistically significant differences between the three groups. Patients with periodontitis and dento-maxillary anomalies (DMAn) had a significantly higher bacterial concentration compared to the other two groups.

For *Treponema denticola* (p=0.004), the differences between groups were also statistically significant. Post hoc tests revealed that patients with periodontitis and DMAn had a significantly higher concentration (median = 4.32, IQR = 2.77-5.54) compared to patients without periodontitis and DMAn (median = 0, IQR = 0-0.96) (p=0.003).

Unlike the red complex bacteria with increased pathogenicity, the concentration of *Aggregatibacter actinomycetemcomitans* did not show statistically significant differences between the three groups.

The analysis of bacteria with moderate pathogenicity, specifically the orange complex, showed that *Eikenella corrodens* (p=0.037), *Campylobacter rectus* (p<0.001), and *Fusobacterium nucleatum* (p=0.015) exhibited statistically significant differences. However, for *Prevotella intermedia* and *Prevotella nigrescens*, the differences between the groups were not statistically significant.

While *Eikenella corrodens* only showed a trend towards statistical significance (possibly due to the small sample size), it had a higher concentration in patients with

periodontitis and DMAn compared to patients without periodontitis and DMAn (p=0.091) or patients with periodontitis but without DMAn (p=0.099).

*Campylobacter rectus* demonstrated that patients with periodontitis and DMAn had a significantly higher concentration compared to patients without periodontitis and DMAn (p=0.006), and patients with periodontitis but without DMAn (p=0.002).

*Fusobacterium nucleatum* revealed that patients with periodontitis and DMAn had a significantly higher concentration compared to those without periodontitis and DMAn (p=0.047), suggesting its important role in the exacerbation of periodontal inflammation in the presence of DMAn.

The analysis of bacteria with low pathogenicity showed that all green complex bacteria, including *Capnocytophaga ochracea* (p=0.008), *Capnocytophaga sputigena* (p=0.014), and *Capnocytophaga gingivalis* (p=0.010), presented statistically significant differences. Patients with periodontitis and DMAn had significantly higher bacterial concentrations of *Capnocytophaga ochracea*, *Capnocytophaga sputigena*, and *Capnocytophaga gingivalis* compared to those without periodontitis and DMAn.

Additionally, *Capnocytophaga gingivalis* exhibited a significantly higher concentration in patients with periodontitis and DMAn (median = 5.87, IQR = 5.34-6.04) compared to patients with periodontitis but without DMAn (median = 4.41, IQR = 3.5-5.71) (p=0.025).

Patients in Group 1 (PD and DMAn) presented significantly higher concentrations of *Treponema denticola*, *Tannerella forsythia*, *Porphyromonas gingivalis*, *Campylobacter rectus*, *Fusobacterium nucleatum*, *Capnocytophaga ochracea*, *Capnocytophaga sputigena*, and *Capnocytophaga gingivalis* compared to patients in Group 2 (PD without DMAn) and Group 3 (Healthy).

Patients in Group 2 (PD without DMAn), although they did not show statistically significant differences, exhibited slightly higher concentrations of *Aggregatibacter actinomycetemcomitans*, *Treponema denticola*, *Tannerella forsythia*, *Eikenella corrodens*, *Fusobacterium nucleatum*, *Capnocytophaga ochracea*, and *Capnocytophaga sputigena* compared to Group 3 (Healthy). Conversely, *Porphyromonas gingivalis*, *Campylobacter rectus*, and *Capnocytophaga gingivalis* were slightly lower in concentration in Group 2 compared to Group 3.

Patients in Group 3 (Healthy) exhibited very low concentrations of the studied pathogenic bacteria compared to both Group 1 (PD and DMAn) and Group 2 (PD without DMAn).

The comparative analysis between Group 2 (PD without DMAn) and Group 3 (Healthy) showed that patients in Group 2 had higher concentrations of periodontopathogenic bacteria compared to healthy patients in Group 3. However, these differences were not statistically significant for most bacterial strains. Notably, for *Porphyromonas gingivalis*, *Campylobacter rectus*, and *Capnocytophaga gingivalis*, concentrations were slightly higher in Group 3 compared to Group 2, but without statistical significance.

The comparative analysis between Group 1 (PD and DMAn) and Group 2 (PD without DMAn) revealed that patients in Group 1 had significantly higher concentrations of *Tannerella forsythia*, *Porphyromonas gingivalis*, *Campylobacter rectus*, and and *Capnocytophaga gingivalis* compared to patients in Group 2 (PD without DMAn). Additionally, *Eikenella corrodens* and *Capnocytophaga sputigena* showed a trend towards statistical significance, indicating higher concentrations in Group 1, though not reaching significance. Other bacterial species such as *Treponema denticola*, *Fusobacterium nucleatum*, *Capnocytophaga ochracea*, *Aggregatibacter actinomycetemcomitans*, *Prevotella intermedia*, and *Prevotella nigrescens* did not exhibit statistically significant differences between the two groups, although their concentrations tended to be higher in Group 1.

In conclusion, patients in Group 1 (PD and DMAn) displayed significantly higher concentrations of periodontopathogenic bacteria compared to those in Group 2 (PD without DMAn) and Group 3 (Healthy). This indicates that the presence of dento-maxillary anomalies significantly contributes to the increased bacterial load.

The qualitative analysis of highly pathogenic bacteria revealed no significant differences in the distribution of *Aggregatibacter actinomycetemcomitans* between the analyzed groups ($p=0.238$).

However, the distribution of bacteria from the red complex (*Treponema denticola*, *Tannerella forsythia*, and *Porphyromonas gingivalis*) showed significant differences between the groups.

In the case of *Treponema denticola*, 60% of patients in Group 1 (periodontitis with dento-maxillary abnormalities) had high concentrations, compared to only 10% in Group 2 (periodontitis without dento-maxillary abnormalities). Additionally, *Treponema denticola* was undetectable in 60% of patients in Group 3 (without periodontitis and dento-maxillary abnormalities), further highlighting the significant differences between groups.

Regarding *Tannerella forsythia*, all patients in Group 1 and 80% of patients in Group 2 showed high concentrations. In Group 3, the distribution was equal, with 50% of patients having high concentrations and 50% low concentrations.

For *Porphyromonas gingivalis*, 90% of patients in Group 1 showed high concentrations, while only 30% of patients in Group 2 had similar levels. In Group 3, no patients exhibited high concentrations, with over 90% showing low values.

In conclusion, patients in Group 1 (periodontitis with dento-maxillary abnormalities) had the highest prevalence of elevated concentrations of red complex bacteria compared to Group 2 (periodontitis without dento-maxillary abnormalities) and Group 3 (without periodontitis and dento-maxillary abnormalities). This underscores the association between dento-maxillary abnormalities and increased bacterial load, particularly for highly pathogenic bacteria.

The distribution of patients across the analyzed groups and the concentrations of bacteria from the orange complex (*Eikenella corrodens*, *Prevotella intermedia*, and *Fusobacterium nucleatum*) revealed significant differences between the groups, unlike *Campylobacter rectus* and *Prevotella nigrescens*, which did not show such differences.

For *Eikenella corrodens*, all patients in Group 1 (periodontitis with dento-maxillary abnormalities) and Group 2 (periodontitis without dento-maxillary abnormalities) had low or undetectable concentrations. In contrast, Group 3 (without periodontitis and dento-maxillary abnormalities) displayed a mix, with 80% of patients showing low or undetectable concentrations, while 20% had high concentrations, highlighting significant differences between the groups.

Regarding *Prevotella intermedia*, 60% of patients in Group 1 exhibited high concentrations, while only 10% of patients in Group 2 and Group 3 recorded such values, emphasizing the significant differences between the groups.

For *Fusobacterium nucleatum*, 40% of patients in Group 1 and 30% of patients in Group 2 showed high concentrations. In contrast, all patients in Group 3 had low concentrations, which further underscores the significant differences between the groups.

The analysis of patient distribution and bacterial concentrations from the green complex revealed significant differences between groups only for *Capnocytophaga sputigena*, while *Capnocytophaga ochracea* and *Capnocytophaga gingivalis* did not show such differences.

For *Capnocytophaga sputigena*, 50% of patients in Group 1 exhibited high concentrations, whereas fewer than 10% of patients in Group 2 and Group 3 had similarly

high levels. Additionally, Z-tests with Bonferroni correction confirmed that patients with high concentrations of *Capnocytophaga sputigena* were significantly more likely to have periodontitis and dento-maxillary abnormalities (50% vs. 0%).

In contrast, for *Capnocytophaga ochracea* and *Capnocytophaga gingivalis*, the Fisher test indicated that the differences between groups were not statistically significant, suggesting that these bacteria do not exhibit significant variations in concentration across the studied groups.

**Conclusions**

1. High pathogenicity bacteria: *Tannerella forsythia* and *Porphyromonas gingivalis* demonstrated statistically significant differences. Patients with periodontal disease (PD) and dento-maxillary anomalies (DMAn) exhibited significantly higher bacterial concentrations compared to patients in the other two groups.
2. No significant differences: *Aggregatibacter actinomycetemcomitans* did not display statistically significant differences between the study groups.
3. Moderate pathogenicity bacteria: *Eikenella corrodens*, *Campylobacter rectus*, and *Fusobacterium nucleatum* presented statistically significant differences. Patients with PD and DMAn had significantly increased concentrations compared to those without PD and DMAn.
4. Non-significant differences: *Prevotella intermedia* and *Prevotella nigrescens* did not show statistically significant differences between the study groups.
5. Low pathogenicity bacteria: *Capnocytophaga ochracea*, *Capnocytophaga sputigena*, and *Capnocytophaga gingivalis* exhibited statistically significant differences. Patients with PD and DMAn had significantly higher bacterial concentrations compared to patients without PD and DMAn.
6. *Capnocytophaga gingivalis* recorded a significantly increased concentration in patients with PD and DMAn compared to those with PD but without DMAn.
7. Bacteria without significant differences: *Aggregatibacter actinomycetemcomitans*, *Prevotella intermedia*, and *Prevotella nigrescens* did not display statistically significant differences across the groups.
8. Red complex bacteria: *Treponema denticola*, *Tannerella forsythia*, and *Porphyromonas gingivalis* were significantly associated with PD, particularly in patients with PD and DMAn.

9. Orange complex bacteria: *Prevotella intermedia*, *Fusobacterium nucleatum*, and *Eikenella corrodens* demonstrated significant differences between the groups, being more prevalent in cases of PD associated with DMAn.
10. Green complex bacteria: Significant variations were observed, with *Capnocytophaga sputigena* being more prevalent in patients with PD and DMAn, while *Capnocytophaga ochracea* and *Capnocytophaga gingivalis* did not show significant differences across the three groups.

## Study 3: Study on the Determination of the Inflammatory Genetic Profile through the Analysis of Single Nucleotide Polymorphisms in IL-1A, IL-1B, IL-1RN, IL-6, and TNF-α Interleukins

### Introduction

This study, like the previous one, was conducted at the Faculty of Dentistry of U.M.F. "Carol Davila" University of Medicine and Pharmacy in Bucharest, with the approval of the Scientific Research Ethics Commission (protocol number: 27652/02.02.2024) and in accordance with the Helsinki Declaration of 1975 **[15]**.

The *specific objectives* of this study included: determination of the *IL-1A* rs1800587 polymorphism, through quantitative analysis of the T and C alleles of *IL-1A* rs1800587 and the TT, TC vs. CC genotypes in patients with PD and DMAn compared to patients with PD but without DMAn, determination of the *IL-1B* rs1143634 polymorphism, by quantitative analysis of the T and C alleles of *IL-1B* rs1143634 and the TT, TC vs. CC genotypes in patients with PD and DMAn compared to those with PD but without DMAn, determination of the *IL-1RN* rs419598 polymorphism, through quantitative analysis of the T and C alleles of *IL-1RN* rs419598 and the TT, TC vs. CC genotypes in PD and DMAn patients compared to those with PD but without DMAn, determination of the *IL-6* rs1800795 polymorphism, by quantitative analysis of the C and G alleles of *IL-6* rs1800795 and the CC, GC vs. GG genotypes in patients with PD and DMAn compared to those with PD but without DMAn and Determination of the *TNF-α* rs1800629 polymorphism, by quantitative analysis of the A and G alleles of *TNF-α* rs1800629 and the AA, AG vs. GG genotypes in patients with PD and DMAn compared to patients with PD but without DMAn **[15]**.

### Material and Method

All participants included in the study were divided into two distinct groups:

- Group 1: Patients with dento-maxillary anomalies and periodontal damage
- Group 2: Patients with periodontal disease but without dento-maxillary abnormalities

**Results**

The study of *IL-1A rs1800587* polymorphism indicated that the distribution of IL-1A genotypes among patients with and without dento-maxillary anomalies (DMA) showed an interesting trend. Although the differences were not statistically significant (p=0.057, Fisher's Exact Test), the C/C genotype was more frequent in patients without DMA (90% vs. 40%). Similarly, the T allele tended to be associated with the presence of DMA (p=0.057, Fisher's Exact Test) [15].

The analysis of *IL-1B rs1143634* genotype distribution with respect to DMA showed a trend towards association. Although the differences were not statistically significant (p=0.057, Fisher's Exact Test), there was a tendency for the C/T genotype to be associated with periodontal disease (PD) in the presence of DMA (60% vs. 10%). A similar trend was observed for the T allele (p=0.057, Fisher's Exact Test). The frequencies of the C and T alleles of IL-1B rs1143634, although not statistically significant in this study, showed a visibly higher frequency of the T allele in patients from Cohort 1, with periodontal disease and associated dento-maxillary anomalies [15].

The quantitative analysis of *IL-1RN rs419598* polymorphism showed that the frequencies of C/C, C/T, and T/T genotypes did not differ significantly between groups (p=0.332, Fisher's Exact Test). Additionally, the distribution of the T allele of IL-1RN rs419598 indicated that the presence of this allele did not differ significantly between patients with and without DMA (p=1.000, Fisher's Exact Test).

The combined analysis of *IL-1A rs1800587 or IL-1B rs1143634* polymorphisms indicated a significant association (p=0.020, Fisher's Exact Test) between the presence of the T allele for either of the two genes and PD associated with DMA (70% vs. 10%) [15].

The combined analysis of *IL-1A rs1800587 and IL-1B rs1143634* polymorphisms revealed a statistically significant association between the presence of the T alleles for both genes and PD associated with DMA (p=0.025, Fisher's Exact Test). The data suggest that patients lacking the T allele for either gene had a significantly higher prevalence in Cohort 2, which included patients with PD without DMA (90% vs. 30%).

The quantitative analysis of *IL-6 rs1800795* polymorphism showed significant differences between groups with and without DMA in terms of IL-6 rs1800795 genotypes and alleles. The G/C genotype was significantly more frequent in patients with PD and DMA

(60% vs. 10%, p=0.020), while the G/G genotype was more frequent in patients without DMA (90% vs. 30%). Additionally, allele analysis indicated that the C allele of IL-6 rs1800795 was significantly more frequent in patients with PD and DMA (70% vs. 10%, p=0.020).

The analysis of *TNF-α rs1800629* genotype distribution among patients with and without DMA indicated that the A/G genotype was present in 50% of patients with PD and DMA, while the G/G genotype was present in 100% of patients with PD without DMA. Fisher's Test indicated a statistically significant difference between groups (p=0.033), suggesting that the A/G genotype is associated with a higher probability of developing PD in the presence of DMA.

The analysis of TNF-α rs1800629 allele distribution among patients with and without DMA showed that the A allele was present in 50% of patients with PD and DMA and was absent in those without DMA. This difference was statistically significant (p=0.033), indicating a strong association between the presence of the A allele and PD in conjunction with DMA.

**Conclusions**

1. The T allele and C/T genotype frequencies of the IL-1A rs1800587 and IL-1B rs1143634 polymorphisms were significantly higher in patients with periodontal disease (PD) and dento-maxillary anomalies (DMAn).
2. The C allele and C/C genotype frequencies of the IL-1A rs1800587 and IL-1B rs1143634 polymorphisms were significantly higher in PD patients without DMAn.
3. No statistically significant differences were identified for the IL-1RN rs419598 polymorphism between groups in terms of genotype or allele frequencies.
4. The C allele and G/C genotype frequencies of the IL-6 rs1800795 polymorphism were significantly higher in PD patients with DMAn.
5. The G/G genotype frequency for the IL-6 rs1800795 polymorphism was significantly higher in PD patients without DMAn.
6. The A allele and A/G genotype frequencies of the TNF-α rs1800629 polymorphism were significantly higher in PD patients with DMAn.
7. The G/G genotype frequency of the TNF-α rs1800629 polymorphism was significantly higher in PD patients without DMAn.

# Conclusions, Personal Contributions, and Future Directions for Development

In the current research context, advanced gene sequencing technologies and microbiological analysis at the molecular level open new horizons for understanding and managing periodontal disease (PD).

Personal research has particularly highlighted the essential role of genomic microbiology and the determination of individual inflammatory genomic profiles in identifying susceptibility and progression of periodontal disease in the presence of dento-maxillary anomalies. The results also demonstrate the importance of integrating genomic data into clinical practice, thereby promoting the development of personalized prevention and treatment strategies.

The *contributions of my personal research* materialized in the following:

1. Quantitative and qualitative evaluation of 12 periodontopathogenic bacterial strains belonging to the violet complex (*Aggregatibacter actinomycetemcomitans*), red complex (*Porphyromonas gingivalis*, *Treponema denticola*, and *Tannerella forsythia*), orange complex (*Eikenella corrodens*, *Campylobacter rectus*, *Prevotella intermedia*, *Fusobacterium nucleatum*, and *Prevotella nigrescens*), and green complex (*Eikenella corrodens*, *Campylobacter rectus*, *Prevotella intermedia*, *Fusobacterium nucleatum*, and *Prevotella nigrescens*), using advanced molecular genetics techniques (qRT-PCR) (37-46, 82-83).
2. Determination and comparison of the microbial load of 12 periodontopathogenic bacterial species between the analyzed groups, consisting of patients with periodontal disease (PD) and dento-maxillary anomalies (DMA), patients with PD without DMA, and clinically healthy patients (49-60, 86-97).
3. Determination of patient distribution relative to the analyzed groups (patients with PD and DMA, patients with PD without DMA, and clinically healthy patients) and the concentration of 12 periodontopathogenic bacterial species, belonging to the violet complex (*Aggregatibacter actinomycetemcomitans*), red complex (*Porphyromonas gingivalis*, *Treponema denticola*, and *Tannerella forsythia*), orange complex (*Eikenella corrodens*, *Campylobacter rectus*, *Prevotella intermedia*, *Fusobacterium nucleatum*, and *Prevotella nigrescens*), and green complex (*Eikenella corrodens*, *Campylobacter*

*rectus*, *Prevotella intermedia*, *Fusobacterium nucleatum*, and *Prevotella nigrescens*) (61-72, 98-109).

4. Evaluation of the individual genomic inflammatory profile through the analysis of single nucleotide polymorphisms (SNPs) of interleukins IL-1A rs1800587, IL-1B rs1143634, and IL-1RN rs419598, IL-6 rs1800795, and tumor necrosis factor-alpha (TNF-α) rs1800629 in patients with PD and DMA vs. patients with PD without DMA (127-136).
5. Determination of IL-1A rs1800587, IL-1B rs1143634, and IL-1RN rs419598 polymorphisms through the quantitative analysis of the T, C alleles and genotypes TT, TC vs. CC in patients with PD and DMA vs. patients with PD without DMA (127-134).
6. Determination of IL-6 rs1800795 polymorphism, materialized through the quantitative analysis of C, G alleles and genotypes CC, GC vs. GG in patients with PD and DMA vs. patients with PD without DMA (135, 136).
7. Determination of TNF-α rs1800629 polymorphism, reflected by the quantitative analysis of A, G alleles and genotypes AA, AG vs. GG in patients with PD and DMA vs. patients with PD without DMA (137, 138).
8. Publication of two ISI articles:
    - **Albu ŞD**, Suciu I, Albu CC, Dragomirescu AO, Ionescu E. *Impact of Malocclusions on Periodontopathogenic Bacterial Load and Progression of Periodontal Disease: A Quantitative Analysis.* Microorganisms. 2024 Jul 29;12(8):1553. doi: 10.3390/microorganisms12081553 [14].
    - **Albu ŞD**, Dragomirescu AO, Albu CC, Suciu I, Ionescu E. *Genetic Polymorphisms of Interleukins IL-1A, IL-1B, and IL-1RN in Patients with Periodontal Disease and Dento-Maxillary Anomalies.* Romanian Journal of Oral Rehabilitation. 2024; 16(3): 253-266. doi: 10.6261/RJOR.2024.3.16.27 [15].

*Future Directions of Development*

Moving forward, I aim to expand this scientific research through a more in-depth genomic analysis, including whole-genome sequencing (WGS), whole-exome sequencing (WES), and bioinformatic data interpretation, focused on evaluating the impact of integrating genomic technologies into dental practice. By adopting the most advanced genomic sequencing technologies and cutting-edge bioinformatic tools, my goal is to make *genomic dentistry* a reality in clinical practice. This innovative approach will redefine the standards for the prevention and management of periodontal disease, especially in the context of dento-maxillary anomalies, and will mark a revolutionary leap in genomic

medicine, bringing significant improvements in patients' quality of life and opening new horizons for scientific research.

## References


1. Neela PK, Atteeri A, Mamillapalli PK, Sesham VM, Keesara S, Chandra J, Monica U, Mohan V. Genetics of Dentofacial and Orthodontic Abnormalities. Glob Med Genet. 2020;7(4):95-100. doi: 10.1055/s-0040-1722303.
2. Greening M. Periodontal Disease: Explaining 2017 AAP Guidelines and Treatment Options [Internet]. Today's RDH. 2022. Available from: https://www.todaysrdh.com/periodontal-disease-explaining-2017-aap-guidelines-and-treatment-options/ (Accessed: 18 September 2023).
3. Moreira R da S, de Moura MRB, Mangueira EVC. Prevalence of Malocclusion in Brazil and Associated Factors Among Adolescents 15-19 Years Old [Internet]. Issues in Contemporary Orthodontics. InTech; 2015. Available from: http://dx.doi.org/10.5772/59507
4. Nazir M, Al-Ansari A, Al-Khalifa K, Alhareky M, Gaffar B, Almas K. Global Prevalence of Periodontal Disease and Lack of Its Surveillance. ScientificWorldJournal. 2020 May 28;2020:2146160. doi: 10.1155/2020/2146160.
5. 5Antunes A, Botelho J, Mendes JJ, Delgado AS, Machado V, Proença L. Geographical Distribution of Periodontitis Risk and Prevalence in Portugal Using Multivariable Data Mining and Modeling. Int J Environ Res Public Health. 2022 Oct 20;19(20):13634. doi:10.3390/ijerph192013634.
6. Udoh S, Adukwu E, Varadi A, Saad S. Effectiveness of the Human Oral Microbe Identification Microarray in Identifying Periodontal Pathogens: A Systematic Review. Applied Microbiology. 2022; 2(3):614-625. https://doi.org/10.3390/applmicrobiol2030047
7. Belibasakis GN, Belstrøm D, Eick S, Gursoy UK, Johansson A, Könönen E. Periodontal microbiology and microbial etiology of periodontal diseases: Historical concepts and contemporary perspectives. Periodontol 2000. 2023 Jan 20. doi: 10.1111/prd.12473.
8. Kozak M, Pawlik A. The Role of the Oral Microbiome in the Development of Diseases. International Journal of Molecular Sciences. 2023; 24(6):5231. https://doi.org/10.3390/ijms24065231

9. Yuan S, Fang C, Leng WD, Wu L, Li BH, Wang XH, Hu H, Zeng XT. Oral microbiota in the oral-genitourinary axis: identifying periodontitis as a potential risk of genitourinary cancers. Mil Med Res. 2021;8(1):54. doi: 10.1186/s40779-021-00344-1.
10. Lakshman Samaranayake. Essential Microbiology for Dentistry 5th Edition. 2018. (Ed) Elsevier, 2018, pp400, ISBN: 9780702074356, eBook ISBN: 9780702075216
11. Uffelmann, E., Huang, Q.Q., Munung, N.S. et al. Genome-wide association studies. Nat Rev Methods Primers 1, 59 (2021). https://doi.org/10.1038/s43586-021-00056-9
12. Hu YJ, Berndt SI, Gustafsson S, Ganna A; Genetic Investigation of ANthropometric Traits (GIANT) Consortium; Hirschhorn J, North KE, Ingelsson E, Lin DY. Meta-analysis of gene-level associations for rare variants based on single-variant statistics. Am J Hum Genet. 2013 Aug 8;93(2):236-48. doi: 10.1016/j.ajhg.2013.06.011.
13. Moreno Uribe LM, Miller SF. Genetics of the dentofacial variation in human malocclusion. Orthod Craniofac Res. 2015;18 Suppl 1(0 1):91-99. doi: 10.1111/ocr.12083.
14. **Albu ŞD**, Suciu I, Albu CC, Dragomirescu AO, Ionescu E. Impact of Malocclusions on Periodontopathogenic Bacterial Load and Progression of Periodontal Disease: A Quantitative Analysis. Microorganisms. 2024 Jul 29;12(8):1553. doi: 10.3390/microorganisms12081553.
15. **Albu ŞD**, Dragomirescu AO, Albu CC, Suciu I, Ionescu E. Genetic Polymorphisms Of Interleukins IL-1A, IL-1B, and IL-1RN in patients with periodontal disease and dento-maxillary anomalies. Romanian Journal of Oral Rehabilitation. 2024; 16(3): 253-266. doi: 10.6261/RJOR.2024.3.16.27
16. National Center for Biotechnology Information, U.S. National Library of Medicine. SNP - rs1800587 [Internet]. Bethesda (MD): National Center for Biotechnology Information, U.S. National Library of Medicine; [cited 2024 Aug 31]. Available from: https://www.ncbi.nlm.nih.gov/snp/rs1800587
17. National Center for Biotechnology Information, U.S. National Library of Medicine. SNP - rs1143634 [Internet]. Bethesda (MD): National Center for Biotechnology Information, U.S. National Library of Medicine; [cited 2024 Aug 31]. Available from: https://www.ncbi.nlm.nih.gov/snp/rs1143634
18. National Center for Biotechnology Information, U.S. National Library of Medicine. SNP - rs419598 [Internet]. Bethesda (MD): National Center for Biotechnology Information, U.S. National Library of Medicine; [cited 2024 Aug 31]. Available from: https://www.ncbi.nlm.nih.gov/snp/rs419598

19. National Center for Biotechnology Information, U.S. National Library of Medicine. SNP - rs1800795 [Internet]. Bethesda (MD): National Center for Biotechnology Information, U.S. National Library of Medicine; [cited 2024 Aug 31]. Available from: https://www.ncbi.nlm.nih.gov/snp/rs1800795
20. National Center for Biotechnology Information, U.S. National Library of Medicine. SNP - rs1800629 [Internet]. Bethesda (MD): National Center for Biotechnology Information, U.S. National Library of Medicine; [cited 2024 Aug 31]. Available from: https://www.ncbi.nlm.nih.gov/snp/rs1800629