ORAL HEALTH OUTCOMES AS POTENTIAL INDICATORS OF CANCER EXPERIENCE

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According to an estimate from the American Cancer Society in 2018, 1,735,350 people were expected to be diagnosed with cancer in the United States, with 609,640 dying from the disease. The late diagnosis of cancer has a negative impact on the health care system due to higher treatment cost and decreased chances of favorable prognosis. Due to the nature of their profession, dentists and their teams are well positioned to identify oral risk markers related to cancer, which increases the potential for early diagnosis and chances of survival. For example, tooth agenesis has been associated with increased risk for ovarian cancer. A greater awareness of oral conditions that are linked to genetic predictors of cancer susceptibility will provide dentists an opportunity to improve patient outcomes by suggesting genetic screenings for prevention. The objective of this study is to identify craniofacial conditions that might be risk markers for cancers by performing association studies and approaches such as a phenome-wide association study (PheWAS) including orofacial phenotypes. A PheWAS can determine if clinical traits (phenotypes) or specific diagnosis are associated with a given genetic variant. Hence, this study will evaluate if selected single nucleotide polymorphisms (SNPs) present in cell regulatory gene pathways are associated with orofacial conditions affecting the study population; determine whether there is an increased frequency of these conditions among individuals who have been diagnosed with cancer compared to healthy controls; and identify the range of head and neck conditions associated with the selected SNPs through a PheWAS approach. All samples were obtained through the Dental Registry and

DNA Repository (DRDR) at the University of Pittsburgh, School of Dental Medicine. DNA was extracted from whole saliva using established protocols and genotyping data from over 3,000 individuals were generated using TaqMan chemistry. PLINK software was used to perform allele frequency tests and a logistic regression using R environment was performed taking covariates such as ethnicity and gender into account. We found several genetic associations with the phenotypes of interest that were later confirmed with the PheWAS approach. Additionally, novel associations that can potentially be markers of cancer risk were found.

Table of Contents

List of Tables

List of Figures

Preface

I've been blessed by many amazing people during my academic journey. I would like to first thank my mentor Dr. Alexandre Vieira who inspired me to learn more about the genetics of human diseases and since we first met 8 years ago, has been my main example of leadership and mentorship. I am grateful for my committee members Dr. Adriana Modesto, Dr. Napierala Dobrawa and Dr. Juan Taboas for their guidance, patience and support during the PhD process. I am also grateful for Dr. Ouyang HongJiao, Dr. Giuseppe Intini, Dr. Alejandro Almarza and Dr. Elia Beniash for their feedback, insights and help with my project.

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My project would not be possible without the volunteers of the Dental Registry and DNA Repository, so I would like to express my appreciation for their participation.

I thank God and my family for all the love and support during these past 4 years. My parents Fernanda and Max Lucas, and sister Priscilla could not be more supportive and present even with the geographic distance. My husband Kyle Chappel and his (our) family were my main base here in Pittsburgh, and I could not have done it without them. During this journey I received my greatest gift which is my daughter Mia Marie, she has been my motivation to keep strong even during this difficult pandemic.

1.0 INTRODUCTION

1.1 Cancer Epidemiology and Potential Markers

Cancer is one of the deadliest diseases and it affects a great number of people worldwide (Witsch, Sela, and Yarden 2010). It is a complex disease based on a process that drives the transformation of normal cells into their malignant derivatives (Witsch, Sela, and Yarden 2010). Approximately 38.4% of people will be diagnosed with some form of cancer in their lifetime (Noone 2018). Survival rates vary depending on the type of cancer and the stage at diagnosis. Earlier stage diagnosis increases the likelihood of successful treatment and survival rates (Noone 2018). Nevertheless, because early cancers can be difficult to detect, much focus has been placed on the identification of more easily detectable cancer *risk markers*. A risk marker is a physiologic or anatomical characteristic that indicates a genetic tendency of developing the disease in question. The *BRCA1* and *BRCA2* genes are examples of genetic risk markers whose pathogenic variants can cause a significant increased risk of breast and ovarian cancer (Santana Dos Santos et al. 2018). Additionally, several phenotypic risk markers (i.e., clinical traits), such as anatomical craniofacial abnormalities, have also been associated with an increased likelihood of developing cancers (Obermair et al. 2019; Machado et al. 2017; Dunkhase et al. 2016; Cordero and Varela-Calvino 2018; Shi et al. 2018; Corbella et al. 2018; Fekonja, Cretnik, and Takac 2014; Lammi et al. 2004). For example, cleft lip/palate has been found to be associated with diffuse gastric cancer (Obermair

et al. 2019), breast cancer (Machado et al. 2017), squamous cell carcinoma of the skin and others (Dunkhase et al. 2016). Additional studies reported associations between periodontitis and colorectal cancer (Cordero and Varela-Calvino 2018), breast cancer (Shi et al. 2018) or any type of cancer (Corbella et al. 2018). Lastly, hypodontia (a disorder of tooth development) has been correlated with risk for epithelial ovarian cancer (Fekonja, Cretnik, and Takac 2014) and colorectal cancer (Lammi et al. 2004). These previous reports point towards the hypothesis that orofacial phenotypes are related to cancer risk independent to cancer type. In other words, we can predict risk for cancer through the presence of genetic variants or through visual anatomical characteristics/ phenotypic traits that have been linked to an increased risk of developing the disease.

The mechanistic understanding of cancer and clinical traits concurrences could be explained by genetic and non-genetic factors or the interaction of both factors. For molecular link between congenital abnormalities and cancer, the homeobox containing genes and the results of fusion events between growth factors and transcription factors have been suggested as culprits of unregular cell growth (Bille et al. 2005; Anbazhagan and Raman 1997; Cillo et al. 1999). Another possible mechanistic link could be through environmental factors such as carcinogens acting as teratogens as well (Bille et al. 2005).

1.2 The Role of Oral Health Professionals in Cancer Prevention

Challenges faced by oral health professionals include determining what factors are causing oral diseases, what the consequences are of preexisting systemic conditions and understanding how a disease can lead to another and determining a definite diagnosis. As a routine visit to the

dentist includes examination of the oral cavity and head and neck structures, these professionals are well positioned to identify risk markers and phenotypic traits linked to cancer. A better understanding of a set of orofacial phenotypes that are markers for cancer risk could enable dentists and allied health care professionals to identify high risk patients. Furthermore, greater awareness of oral conditions that are linked to genetic predictors of cancer susceptibility will provide dentists an opportunity to improve patient outcomes by suggesting screenings for prevention.

Oral health professionals may also encounter adverse oral health outcomes as a result of cancer treatment. Chemotherapy and radiotherapy may affect individual's immunity and, as consequence, change the pattern of their oral health, with individuals showing more problems and not responding as well as they might to the traditional dental treatments. Xerostomia, infection, abnormal tooth development, taste alteration and mucositis are within the most common oral related complications of cancer treatment (Han 2017). Treatments for head and neck carcinomas, specifically include a combination of surgery, radiation, and/or chemotherapy. This multimodal therapy can result in pain and fibrosis in structures involved with chewing, swallowing and talking, causing problems such as nutritional deficiencies, oral health related issues and communication impairment (A. Harris et al. 2020). The oral complications listed above can appear as consequences of cancer treatment however, some of them and different oral diseases appear before cancer diagnosis and could serve as cancer risk markers.

1.3 Precision Medicine and Phenome-Wide Scan Approach

Precision medicine is a relatively novel field seen as a hope to better overcome the aforementioned challenges. It takes into account individuals' variability, such as their individual

genetics, environment and lifestyle to find individualized measures of disease prevention and treatments (Walji, Karimbux, and Spielman 2017). In order to successfully apply precision medicine, one needs to understand genotype-phenotype interactions, through the generation of phenomic-level data that will allow us to study which genomic variants affect phenotypes (Musunuru et al. 2018). Furthermore, this allows for a broader understanding of pleiotropy, which is when one gene appears to affect more than one disease or phenotypic trait (Houle, Govindaraju, and Omholt 2010). There are two main methodologies used to detect gene-disease associations: an approach testing gene variants that can associate to one phenotype [targeted or genome-wide association studies (GWAS)] and an approach testing multiple phenotypes that can associate to one or more genetic variant (phenome-wide association studies or PheWAS). GWAS has proven to be an efficient method of identifying associations between gene variants, including single nucleotide polymorphisms (SNPs) and specific diseases. PheWAS is essentially "reverse GWAS" whereby one can determine the range of clinical traits (phenotypes) associated with a given genotype (Denny et al. 2010). Previous studies have shown the feasibility and success of the PheWAS technique to identify multiple associations from well-powered samples (Denny et al. 2010; Karnes et al. 2017; Pathak et al. 2012; Namjou et al. 2014) and provide novel insights not readily attainable by forward-genetic strategies. A unique quality of the PheWAS technique is its capacity to evaluate cross-phenotype associations (Hebbring 2019). On the other hand, a similarity between PheWAS and different types of association studies is that they are not intended to establish disease causation between variants and traits or conditions, but rather to help create hypotheses about causal factors for the phenotypes (Musunuru et al. 2018).

1.4 Oral Conditions, Systemic Diseases and Gene Pathways Involved

The most common and most studied oral conditions so far include dental caries and periodontal disease, both bacteria-mediated infections (Peres et al. 2020). Efforts such as water fluoridation, oral hygiene-based preventive strategies and more aggressive treatment approaches are indicated to mitigate and treat dental caries and periodontal disease. Symptoms for these distinct conditions can be similar, such as developing discomfort, pain, and inflammation and individuals affected by these conditions are also usually more susceptible to additional health problems. Dental caries is the most prevalent oral disease and second in the number of people it affects worldwide (Edelstein 2006). Dental caries development involves host susceptibility and environmental factors such as sugar intake. Bacteria present in the mouth make acids that start destroying the tooth enamel and eventually all tooth structures. An extreme outcome of dental caries is tooth loss but this condition can also lead to infection and pain (Silk 2014).

Similarly, periodontal disease is considered a big threat to oral health and the major cause of tooth loss (Zhao et al. 2018; Benjamin 2010). It is a chronic inflammatory disease identified by the destruction of the tooth-supporting tissues including periodontal-ligament, alveolar bone, and cementum. Associations between periodontitis and different systemic conditions are established (Chatzopoulos et al. 2018). More specifically diabetes mellitus (Stanko and Izakovicova Holla 2014), cardiovascular disease (Lockhart et al. 2012), osteoporosis (Ayed et al. 2018), and rheumatoid arthritis (Golub et al. 2006) have been associated with periodontitis.

Overtime, a chronic inflammatory state of both untreated dental caries and periodontal disease can lead to inadequate amino acid supply, which lead to reduced protein synthesis and degradation (Mercier et al. 2002). Certain pathways that regulate protein synthesis are believed to influence multiple conditions, including metabolic disorders, type 2 diabetes and cancers (Rivera

Rivera et al. 2016). Some of these specific pathways that haven't been as much studied regarding the genetics of the most prevalent oral conditions include the mammalian target of rapamycin (*mTOR*) and the endoplasmic reticulum stress (ER stress) – the first is a master regulator of protein synthesis, composed by Tuberous sclerosis 1 and 2 (*TSC1* and *TSC2*) which are tumor suppressor genes. When these genes are activated, *mTOR* function is repressed, and when *TSC1* and *TSC2* are defective, such as in the tuberous sclerosis complex disease, these genes lose their function, leading to hypermineralization of bones. *MTOR* signaling is comprised of two complexes – mammalian target of rapamycin complex 1 (*mTORC1)* and mammalian target of rapamycin complex 2 (*mTORC2),* the first is a center regulator for protein synthesis and the second is a center regulator for the serine/threonine kinase (AKT) in the cell. *RHEB* (Ras homolog enriched in brain) is a positive regulator for both *mTORC1* and *mTORC2*, but its function is repressed by *TSC1* and *TSC2* (Brown et al. 1994). In many oncogenes mutated pathways such as the *PI3K/AKT* pathway, *mTORC1* acts as a downstream effector, resulting in *mTORC1* hyperactivation in a high number of human cancers (Hua et al. 2019).

Activation of the *mTOR* signaling by alcohol use can inhibit mineralization and odontogenic differentiation of human dental pulp cells, negatively regulating dental pulp repair (Qin et al. 2017). A recent study has shown that when *mTOR* signaling is inhibited, there is an alleviation of the inflammatory response to periodontal pathogens such as *Porphyromonas gingivalis* (Xia et al. 2017), what led us to believe that variation in *mTOR* signaling genes will play a role in periodontal disease outcomes.

ER stress on the other hand is a phenomenon that occurs when signals emanating from the endoplasmic reticulum induce a transcriptional program that enables cells to survive the stress generated by an elevated amount of protein synthesized (Schonthal 2012). When affected cells

sense there is ER stress, three signal pathways can be activated: ER transmembrane inositol-requiring enzyme 1 (*IRE1*) α and β, protein kinase-like ER kinase, and activating transcription factor 6 (*ATF6*) (Reimold et al. 2000). Collectively, these pathways can restore intracellular homeostasis. This coordinated response, the unfolded protein response (UPR), facilitates the folding, processing, export, and degradation of proteins emanating from the endoplasmic reticulum during stressed conditions (Ron and Walter 2007). *IRE1* is an endoplasmic reticulum membrane domain, which has a dual function of making apoptosis and serving as an endoribonucleous. *IRE1* splices a 26-base pair sequence of *Xbp1* (Yoshida et al. 2001). *Xbp1* can control many genes that are involved in the biogenesis of ER as well as protein folding. In addition, *Xbp1* expression was also demonstrated to play a role in ameloblasts endoplasmic reticulum volume during enamel formation (Tsuchiya et al. 2008). This pathway is essential to maintain intracellular homeostasis and in conditions such as in diabetes, research has shown that ER stress modulation is possible through *mTOR* signaling. This approach is effective in suppressing insulin resistance and obesity and shows an interplay between ER stress and *mTOR* signaling (J. Wang, Yang, and Zhang 2016).

The conditions we are studying here are complex with variable levels of genetic influences that modulate both the development of underlying affected structures and active protein synthesis, including folding and transport, which are mechanisms not well understood in regards to pathogenesis of each oral disease.

1.5 Hypotheses and Specific Aims

We hypothesized that:

1 - Variations in genes belonging to the *mTOR* and ER stress pathways play a role in oral and bone diseases.

In this section, the first specific aim was to evaluate the presence of these associations by comparing the frequency of the selected variants in both affected and unaffected groups of individuals for each disease. We generated genotyping data for SNPs present in the *mTOR* and ER stress pathways. Successfully identifying associations provides insights regarding the etiology of each studied condition and better ways of diagnosing and preventing them. The second specific aim was to determine if associations could be better detected when individuals concomitantly affected by more than one disease are analyzed in combination. Our intention was to verify potential pleiotropic effects between the studied genes and conditions.

2 – After finding positive results in the first hypothesis we then hypothesized that: A range of orofacial phenotypes may be associated with cancer directly, or indirectly through cancer associated genes. The results of this section would contribute in determining which patients are at higher risk for this condition. To the best of our knowledge, this was the first time a PheWAS was applied to oral health outcomes, to identify clinical cancer risk markers. We performed a PheWAS to identify patterns of disease in individuals who have been diagnosed with cancer. This approach is efficient because it identifies a myriad of associations utilizing a large dataset comprised of genetic data in combination with electronic health records information.

In this section, the first specific aim was to evaluate the frequency of the most common orofacial conditions present in individuals who have been diagnosed with cancer and to compare those with an unaffected group of individuals using deidentified electronic health record data. In this epidemiological analysis we are searching direct associations between cancer and oral

phenotypes. Second, we aimed to perform a phenome-wide association study (PheWAS), utilizing head and neck clinical information, focusing on individuals who had cancer to identify the range of different phenotypes associated with specific SNPs that are also associated with cancers. In this indirect analysis we are searching for associations through a genetic component in common between conditions. This scientific knowledge changes clinical practice because identification of individuals carrying phenotypic or genotypic markers allow dentists to refer them for screenings or checkups more frequently. This conduct increases the possibility of diagnosing cancers at early stages when the treatment survival rates are higher.

2.0 INVESTIGATING WHETHER VARIATION IN MTOR AND ER STRESS GENES ARE ASSOCIATED WITH ORAL AND BONE PHENOTYPES

2.1 FOREWORD

This chapter is adapted from a previously published manuscript in the Caries Research Journal. Bezamat Mariana, Deeley Kathleen, Khaliq Shahryar, et al. 2018. Are mTOR and Endoplasmic Reticulum Stress Pathway Genes Associated with Oral and Bone Diseases? Caries Research.

2.2 SUBJECTS AND METHODS

Twenty-seven markers in eight genes of the *mTOR* and ER stress pathways were selected in order to be tested in five oral/bone disease phenotypes (dental caries, periapical lesions due to deep caries lesions in dentin, periodontitis, osteoporosis, and temporomandibular joint symptoms), described in detail below. In this cohort study, a dataset consisting of DNA samples from 3,912 unrelated subjects who sought treatment at the University of Pittsburgh dental clinics was utilized. Individual samples and clinical history were obtained through the Dental Registry and DNA Repository (DRDR) of the School of Dental Medicine, University of Pittsburgh. Subjects' mean age was 40.9 ± 19.3 years (ranging from 6 to 92 years-old). This project has the approval of the University of Pittsburgh Institutional Review Board (IRB # 0606091). Written informed consent

documents were obtained from all subjects. Age appropriate assent documents were used for children between 6 and 14 years and signed informed consent documents were obtained from the parents. For all comparisons described below, there were no significant differences in the distribution of ages and the frequency of self-reported White and Black patients between the two comparison groups.

2.2.1 **Phenotypes and Sample Selection**

Extraction of clinical data was carried out after calibration by an experienced specialist. Clinical data included a complete list of oral conditions and treatments present in the database for each of the patients seeking care between September 2006 and January 2013. The intra-examiner agreement was assessed by a second extraction of clinical data in 10% of the sample after 2 weeks, with a kappa of 1.0. Since each phenotype studied is recovered from a registry of clinical information derived from the dental clinics of the University of Pittsburgh, calculating inter or intra-examiner agreement was not possible. All phenotypes are recorded following the same guidelines by students in training under the supervision of experienced dental professionals who are calibrated annually.

2.2.2 **Dental Caries**

We selected 1,481 samples (715 males and 766 females) to evaluate dental caries. The presence and severity of dental caries was taken into consideration and we used the decayed, missing due to caries and filled teeth (DMFT/dmft) score to assign individuals to one of the comparison groups. The population was classified as either having ‘less severe’ (N=553) or ‘more

severe' (N=853) caries experience, based on DMFT/dmft distribution (DMFT/dmft mean and standard deviation) and subject's age. The mean DMFT score was 15.9 with a standard deviation of 8.7 and ranged from 0 to 28. The criteria used here for classification of caries experience took age into consideration, since it is expected that caries experience will increase in the general population with age (Liss et al. 1982). Drinking water in the Pittsburgh area is artificially fluoridated. Table 1 describes the criteria defining individuals with higher or lower caries experience. This study sample was previously described (Kuchler et al. 2014).

Table 1. Definition of caries experience based on age and DMFT scores. The thresholds were defined based on the DMFT distribution in the studied group by age.

Caries Experience Level	DMFT/dmft
Children and teenagers (from 6 to 19 years of age)	
Less Severe Caries Experience	0-3
More Severe Caries Experience	4 or higher
Young Adults (from 20 to 39 years of age)	
Less Severe Caries Experience	0-10
More Severe Caries Experience	11 or higher
Middle Age (from 40 to 59 years of age)	
Less Severe Caries Experience	0-15
More Severe Caries Experience	16 or higher
Elderly (60 years of age and older)	
Less Severe Caries Experience	0-20
More Severe Caries Experience	21 or higher

Power calculations (Purcell et al. 2007), assuming that our marker alleles were in complete linkage disequilibrium with the genetic variant contributing to caries susceptibility, and that the

chance of having a distinct (very low or very high) caries susceptibility increased two and a half-fold when having one copy of the caries susceptibility allele, suggested a 92% power to detect a possible association with our sample size. This procedure was for a marker B in linkage disequilibrium with our test locus A. Other parameters specified in the calculations were the high-risk allele frequency for the allele A (set at 0.1); the disease prevalence in the general population [set at 0.5, corresponding to the approximate frequency of caries-free individuals or highly affected individuals (DMFT=20)], and the genotype risks for the Aa and AA genotypes relative to the baseline aa genotype risk. We used most of the same power parameters for all five phenotypes (dental caries, periodontitis, periapical pathology, osteoporosis, and temporomandibular joint discomfort).

2.2.3 **Periapical Lesions Due to Deep Carious Lesions in Dentin**

Sixteen hundred radiographic records were screened for subjects with deep carious lesions in dentin with or without periapical lesions (≥3mm in diameter). The criteria used to select the affected group was the presence of both deep carious lesions and periapical lesions (110 individuals, 57 males and 53 females with an average age of 57 years and a standard deviation of 10 years) and for comparison, we selected a group in which they had the presence of deep carious lesions but absence of periapical lesions (158 individuals, 65 males and 93 females with an average age of 58 years and a standard deviation of 8 years). This cohort of a total of 268 samples has been previously reported (Menezes-Silva et al. 2012). We estimated to have 85% power to detect an association with the studied sample size. The disease prevalence in the general population was set at 0.5, corresponding to the approximate frequency of deep caries lesions and absence of periapical lesions in the study sample.

2.2.4 **Periodontitis**

Individuals were considered affected if presenting at least three teeth exhibiting sites of clinical attachment loss equal or greater to 5 mm in two different quadrants (61 individuals, 22 males and 39 females). For comparison, we selected individuals showing absence of clinical attachment loss and no sites with probing depth greater than 3 mm (325 individuals, 144 males and 181 females) totalizing 386 samples selected for genotyping (average age was 50 years with a standard deviation of 8 years). This sample has been previously described (Letra et al. 2012). Considering a prevalence of periodontitis of 60% (Eke et al. 2012), a power of 80% was estimated for this phenotype in our study sample.

2.2.5 **Osteoporosis**

Twenty-two cases of osteoporosis/osteopenia were identified (20 females and 2 males, mean age of 62 years), and 553 unaffected individuals older than 50 years of age (221 men, 332 women, mean age of 68 years) were selected to serve as comparison. None of the selected cases had periodontitis but seven of those had dental caries and were part of the dental caries group described above as well. We estimated power as 43% with the sample size we had. The prevalence of osteoporosis was set at 0.55, according to the May 2018 Interdisciplinary Symposium on Osteoporosis (nof.org).

2.2.6 **Temporomandibular Joint Symptoms**

We selected 1,202 women in child bearing age, 521 with a record of, at least, one symptom in the temporomandibular joint (clicks, sounds or pain) and 681 without any symptoms that were used for comparison. Their mean age was 35.3 years, ranging from 15 to 55 years. Power was estimated as 100% to detect a possible association with the studied sample size. The disease prevalence in the general population was set at 0.5.

2.2.7 **Combined Phenotypes**

We followed the European Federation of Periodontology (EFP) and European Organization for Caries Research (ORCA) joint recommendation and analyzed dental caries combined with periodontitis within the same individuals (Chapple et al. 2017). In addition, we analyzed dental caries combined with periapical pathology and dental caries combined with periodontitis and periapical pathology within the same individuals (Figure 1). Osteoporosis and temporomandibular joint-symptoms phenotypes were excluded from this analysis since only 22 cases with confirmed osteoporosis/osteopenia were available and for temporomandibular joint symptoms no formal significant associations with the selected genes were found.

We excluded 24 participants that had missing information about the presence of periodontitis or periapical pathology since those conditions were taken into consideration for the combined analyses. We found that 794 individuals had periodontitis and recorded caries experience (high caries experience, 174 females and 149 males; low caries experience, 229 females, 242 males), 433 had periapical pathology and recorded caries experience (high caries experience, 57 females and 63 males; low caries experience, 158 females, 155 males), and 234 had periodontitis, periapical pathology and high caries experience (high caries experience, 31 females and 48 males; low caries experience, 90 females, 107 males). Combining the disease phenotypes aims to generate and evaluate groups that are more susceptible to oral diseases.

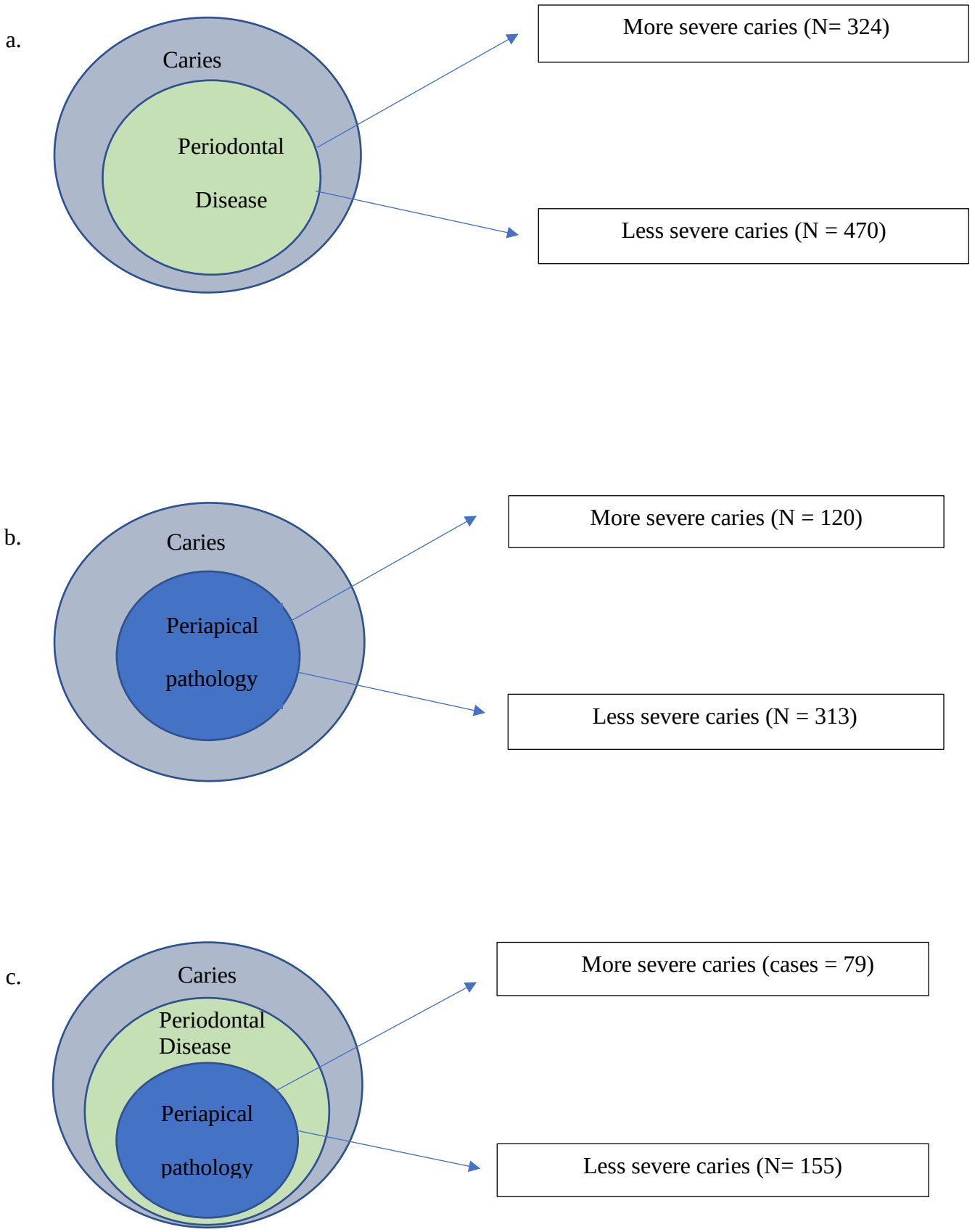

Figure 1. Combined analysis of more severe and less severe caries experience within individuals affected by periodontal disease alone (a), periapical pathology alone (b), and by both periodontal disease and periapical pathology concomitantly (c).

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2.2.8 **Selection of Genes and Single Nucleotide Polymorphisms**

Since *RHEB* is a molecule located at the center of the mTOR pathway and can be repressed by *TSC1 and 2*, we chose genes immediately up and downstream of *RHEB*. *RHEB*'s role also impacts ER stress (Fan et al. 2017). Twenty-seven single nucleotide polymorphisms (SNPs) in eight genes were selected (*IRE1* -rs196929, rs196950, rs11655020, rs16947425 and rs1874087, *XBP1* -rs2097461 and rs2239815, *RPTOR* -rs2289764, rs1012117, rs11651724, rs4255830 and rs4396582, *TSC1* -rs1050700, *TSC2* -rs1051771, rs7187438 and rs2073636, *RHEB* -rs3753151, rs2299967, rs2374261 and rs1109089, *RICTOR* -rs1239265, rs13166875, rs1423688 and rs2043112 and *mTOR* -rs11580061, rs1010447 and rs11121718). We prioritized genes to be studied considering: previous reports of expression in diseased tissues, and previous reports of association with bone diseases. In the case of temporomandibular joint symptoms, four polymorphisms were tested in *IRE1* (rs11655020, rs1874087, rs196950 and rs196929) and two in *XBP1*(rs2097461 and rs2239815).

SNPs were selected based on published reports and/or their locations in the genes, based on their likelihood to have functional consequences (i.e., located in promoter regions, exons or near exon/intron boundaries), or if considered tag SNPs as surrogates for the linkage disequilibrium blocks surrounding the gene of interest, and their minor allele frequencies. We used information from the NCBI dbSNP (http://www.ncbi.nlm.nih.gov/snp) and the HapMap Project (http://www.hapmap.org) databases to select the SNPs for this study.

2.2.9 **Genotyping**

Genomic DNA was extracted from whole saliva using established protocols. Genotypes were generated blindly to clinical diagnosis status. Reactions were carried out using TaqMan chemistry (Ranade et al. 2001) in volumes of 3.0 µl in an ABI PRISM Sequence Detection System 7900 (Applied Biosystems, Foster City, CA, USA). Applied Biosystems supplied assays and reagents. The results were analyzed using SDS software version 1.7 (Applied Biosystems). PCR reactions were repeated twice when necessary.

2.2.10 **Data Analyses**

Allele frequencies and Hardy–Weinberg equilibrium were calculated. Association analyses were performed comparing genotypes between affected individuals and their respective comparison group as implemented in PLINK (Purcell et al. 2007). Assuming that D is the minor allele and d is the major allele, the allelic model compares the frequencies of each allele in each group (D x d), the genotypic model is an additive two degree of freedom model that compares the frequencies of each genotype in the groups (DD x Dd x dd), the dominant model compares the two copies of the common allele frequency versus the other combinations (dd x DD + Dd), and the recessive model compares the two copies of the rare alleles frequency versus the other combinations (DD x Dd + dd). P-values below 0.002 (0.05/27; the denominator is the number of genetic markers tested) were considered statistically significant. Additional analysis was performed combining patients that have more than one oral disease phenotype (periodontitis, periapical pathology, and caries experience), as well as the three oral phenotypes combined.

2.3 RESULTS

We found nominal associations between each of the five phenotypes studied and *mTOR* or ER stress genes. Table 2 shows the summary results for associations between SNPs and the five phenotypes. Complete results can be found in the appendix A table 12. Odds Ratios and 95% confidence intervals were calculated for significant results ($p<0.002$) of 1 degree of freedom comparisons. Significant associations were found between periapical lesions due to deep carious lesions in dentin and *RICTOR* (p=6.341e-017, OR = 18.82, 95% C.I. 9.25 – 38.29), *RHEB* (p=0.0002, OR = 0.71, 95% C.I. 0.45 – 1.11) and *RPTOR* (p=0.00022, OR = 3.55, 95% C.I. 1.77 - 7.10), osteoporosis and *mTOR* (p=5.971e-008, OR = 8.50, 95% C.I. 3.40 – 21.26), *RPTOR* (p=0.001, OR = 0.73, 95% C.I. 0.30 – 1.74), *RICTOR* (p=0.0004, OR = 4.47, 95% C.I. 1.36 – 14.65), *IRE1* (p=0.00021, OR = 2.71, 95% C.I. 1.37 – 5.35), *XBP1* (p=0.00095, OR = 2.76, 95% C.I. 1.34 – 5.65) and *TSC2* (p=1.0e-5, OR = 0.04, 95% C.I. 0.007 – 0.30), and dental caries and *RPTOR* (p=0.00079, OR = 1.50, 95% C.I. 1.18 – 1.91) (Table 2).

In the combined analysis 27% of the patients had concomitant periapical lesions and more severe caries experience, 40% had concomitant periodontal disease and more severe caries experience and 33% had all three diseases concomitantly. When combining patients that had concomitant dental caries and periapical lesions, both tested markers in *RHEB* showed associations, and for the group of concomitant dental caries, periodontitis, and periapical pathology, both markers in *RHEB* and *RPTOR* showed associations (Table 3 and Appendix A Table 12).

Table 2. Summary of results highlighting nominal (between 0.05 and 0.002) and statistically significant (equal or lower than 0.002, marked in bold) p-values for association analyses between periapical lesions, periodontal disease, osteoporosis, dental caries experience, and temporomandibular joint symptoms and the evaluated markers. Assuming that D is the minor allele and d is the major allele, the allelic model compares the frequencies of each allele in each group (D x d), the genotypic model is an additive two degree of freedom model that compares the frequencies of each genotype in the groups (DD x Dd x dd), the dominant model compares the two copies of the common allele versus the other combinations (dd x DD + Dd), and the recessive model compares the two copies of the rare allele frequency versus the other combinations (DD x Dd + dd). Degrees of freedom (DF).

Dental caries									
Gene	**SNP**	**Allele1/2**		**TEST**	**Affected**	**Unaffected**	**X^2**	**DF**	**P-value**
IRE1	rs11655020	A	G	GENO	40/256/240	73/441/303	8.037	2	0.01798
IRE1	rs11655020	A	G	ALLELIC	336/736	587/1047	6.044	1	0.01396
IRE1	rs11655020	A	G	DOM	296/240	514/303	7.965	1	0.00477
RPTOR	rs11651724	A	G	GENO	21/112/170	18/160/353	11.24	2	0.003619
RPTOR	rs11651724	A	G	ALLELIC	154/452	196/866	11.26	1	**0.000791**
RPTOR	rs11651724	A	G	DOM	133/170	178/353	8.876	1	0.002889
RPTOR	rs11651724	A	G	REC	21/282	18/513	5.426	1	0.01984
Periodontal disease									
TSC1	rs1050700	C	T	ALLELIC	39/47	165/317	3.918	1	0.04776
TSC1	rs1050700	C	T	DOM	29/14	123/118	3.947	1	0.04694
IRE1	rs196929	T	C	GENO	14/15/12	37/86/93	6.723	2	0.03468
IRE1	rs196929	T	C	ALLELIC	43/39	160/272	6.842	1	0.008906
IRE1	rs196929	T	C	REC	14/27	37/179	6.273	1	0.01226
IRE1	rs196950	T	C	ALLELIC	57/55	216/316	4.013	1	0.04516
IRE1	rs1874087	C	T	ALLELIC	54/34	145/169	6.341	1	0.0118
IRE1	rs1874087	C	T	DOM	36/8	101/56	4.843	1	0.02777
RPTOR	rs2289764	C	T	ALLELIC	39/45	152/308	5.586	1	0.01811
Periapical Lesions									
RICTOR	rs1239265	A	T	ALLELIC	62/126	10/254	69.87	1	**6.341e-017**
RICTOR	rs1239265	A	T	GENO	10/42/42	2/6/124	68.38	2	**5.461e-016**
RICTOR	rs1239265	A	T	DOM	52/42	8/124	68.31	1	**4.231e-016**
IRE1	rs196950	T	C	ALLELIC	63/89	69/155	4.503	1	0.03383
XBP1	rs2097461	C	T	GENO	8/40/27	18/38/52	6.055	2	0.04844
RHEB	rs3753151	C	T	GENO	2/39/18	33/49/45	17.17	2	**0.00019**
RHEB	rs3753151	C	T	REC	2/57	33/94	13.463	1	**0.0002**
RPTOR	rs2289764	C	T	ALLELIC	79/93	64/150	10.5	1	**0.00119**
RPTOR	rs2289764	C	T	REC	33/57	15/92	13.60	1	**0.000225**
Osteoporosis									
RHEB	rs1109089	T	C	REC	0/19	98/398	4.636	1	0.0313
MTOR	rs11580061	G	A	ALLELIC	7/29	25/881	29.37	1	**5.971e-008**
MTOR	rs11580061	G	A	GENO	3/1/14	0/25/428	55.482	2	**0.000047**
MTOR	rs11580061	G	A	DOM	4/14	25/428	8.36	1	0.00384
MTOR	rs11580061	G	A	REC	3/15	0/453	75.98	1	**0.000032**
RICTOR	rs1239265	A	T	ALLELIC	4/24	14/376	7.253	1	0.007079
RICTOR	rs1239265	A	T	GENO	2/0/12	2/10/183	12.811	2	**0.001653**

RICTOR	rs1239265	A	T	REC	2/12	2/193	12.23	1	**0.00047**
TSC2	rs1051771	C	G	ALLELIC	6/28	66/892	5.645	1	0.0175
TSC2	rs1051771	C	G	GENO	2/2/13	3/60/416	20.417	2	**4.0e-5**
TSC2	rs1051771	C	G	REC	2/15	3/476	20.41	1	**1.0e-5**
RPTOR	rs11651724	A	G	GENO	3/1/11	12/103/234	12.284	2	0.00215
RPTOR	rs11651724	A	G	REC	3/12	12/337	9.984	1	**0.00158**
RPTOR	rs1012117	A	G	GENO	5/5/5	53/213/215	7.015	2	0.02998
RPTOR	rs1012117	A	G	REC	5/10	53/428	7.014	1	0.008085
XBP1	rs2097461	C	T	ALLELIC	19/13	353/667	8.327	1	0.003907
XBP1	rs2097461	C	T	GENO	7/5/4	71/211/228	11.06	2	0.00396
XBP1	rs2097461	C	T	REC	7/9	71/439	10.93	1	**0.00095**
XBP1	rs2239815	C	T	ALLELIC	20/16	383/627	4.564	1	0.03264
XBP1	rs2239815	C	T	REC	7/11	90/415	5.106	1	0.02384
IRE1	rs16947425	A	C	GENO	5/4/10	12/145/320	31.303	2	**5.0e-5**
IRE1	rs16947425	A	C	ALLELIC	14/24	169/785	8.887	1	0.002872
IRE1	rs16947425	A	C	REC	5/14	12/465	31.27	1	**0.00021**
IRE1	rs11655020	A	G	REC	5/12	53/452	5.959	1	0.01464
Temporomandibular joint symptoms									
IRE1	rs1665020	A	G	ALLELIC	185/693	273/823	4.03	1	0.04469
IRE1	rs1665020	A	G	DOM	145/294	220/328	5.297	1	0.02137

Table 3. Summary of all nominal (p-values between 0.05 and 0.002) and significant results from the combined analysis of patients with caries, periodontitis and periapical lesions (bold indicates statistically significant p-values under the threshold 0.002). Assuming that D is the minor allele and d is the major allele, the allelic model compares the frequencies of each allele in each group (D x d), the genotypic model is an additive two degree of freedom model that compares the frequencies of each genotype in the groups (DD x Dd x dd), the dominant model compares the two copies of the common alleles frequency versus the other combinations (dd x DD + Dd), and the recessive model compares the two copies of the rare alleles frequency versus the other combinations (DD x Dd + dd).

	Gene	SNP	P-value	TEST
Patients with Periodontal Disease and Caries	*RPTOR*	rs1012117	0.05	Recessive
	RHEB	rs1109089	0.02	Dominant
	RICTOR	rs1423688	0.03	Recessive
	RPTOR	rs2374261	0.02	Genotype
	RHEB	rs2374261	0.004	Dominant
	RPTOR	rs4396582	0.03	Genotype

	RPTOR	rs4396582	0.03	Dominant
Patients with Periapical Lesions and Caries	*RHEB*	rs1109089	**0.002**	Genotype
	RHEB	rs1109089	**0.0006**	Allelic
	RHEB	rs1109089	**0.0007**	Dominant
	RHEB	rs2374261	0.003	Genotype
	RHEB	rs2374261	**0.0007**	Allelic
	RHEB	rs2374261	**0.001**	Dominant
	IRE1	rs16947425	0.04	Recessive
	IRE1	rs196950	0.04	Allelic
	XBP1	rs2239815	0.04	Dominant
	TSC1	rs1050700	0.04	Genotype
	TSC1	rs1050700	0.04	Allelic
	TSC1	rs1050700	0.01	Recessive
Patients with Periapical Lesions, Periodontitis, and Caries	*RHEB*	rs1109089	0.005	Genotype
	RHEB	rs1109089	0.003	Allelic
	RHEB	rs1109089	**0.001**	Dominant
	RHEB	rs2374261	**0.0009**	Genotype
	RHEB	rs2374261	**0.0003**	Allelic
	RHEB	rs2374261	**0.0002**	Dominant
	IRE1	rs16947425	0.04	Allelic
	RPTOR	rs4396582	**0.001**	Allelic
	RPTOR	rs11651724	0.007	Genotype
	RPTOR	rs11651724	**0.001**	Allelic
	RPTOR	rs11651724	0.002	Dominant

2.4 DISCUSSION

Although caries is most times a preventable disease, it is still very common all over the world. Many factors can play a role in the dental caries phenotype, such as the high level of consumption of sugar and carbs, the oral microbiota, lack of exposure to fluorides from drinking water and/or dentifrices, and poor oral hygiene. Even though fluoridated water is common in most countries, this practice might soon be challenged. Evidence has shown decreased cognitive performance by prenatal exposure to fluoride (Green et al. 2019).

Not only the aforementioned factors contribute for dental caries development, but evidence also suggest that individual genetic variation plays a role in the disease process as well (Vieira et al. 2012). Furthermore, genetic factors related to the host, that are represented by genes involved with enamel formation, saliva composition, dietary preferences, and immune response (Shuler 2001), can be involved in caries susceptibility. Genes in the *mTOR* pathway are involved in dental mineralization (Kim et al. 2011) and hence could contribute to caries susceptibility. In addition, fluoride induces ER stress and interferes with enamel proteinase secretion (Wei et al. 2013), which may result in alterations of enamel structure that can modify individual susceptibility to dental caries.

MTORC1 is a ternary complex containing *mTOR, RPTOR* (Regulatory Associated Protein of *mTOR*) and G-BetaL. *MTORC1* regulates VEGF (Vascular Endothelial Growth Factor) by inducing HIF1α (Brugarolas et al. 2003). The association between genetic variation in *RPTOR* and cases with more severe caries experience may be related to a mechanism that involves individuals more susceptible to carious lesion progression in enamel and dentine.

When the dental caries phenotype is defined as having caries or not having caries, DMFT score 0 versus DMFT score 1 or higher, it may not be feasible to detect genes that may contribute

to the severity of the disease. This is probably the general limitation of the work done by us and others, both including candidate gene approaches (Tannure, Kuchler, Falagan-Lotsch, et al. 2012; Tannure, Kuchler, Lips, et al. 2012) and genome wide scan analyses (Shaffer et al. 2011; X. Wang et al. 2012). If anybody with any recorded DMFT score is assigned to the disease group, this group will have individuals with very little caries experience (DMFT scores 1 or 2) along with individuals with much higher DMFT scores. We believe a DMFT score of 1 is not under the same influences of a DMFT score of 10, having one decayed tooth is much less of a severe disease than having 10 teeth affected for example. Although it may be surprising for many, Pittsburgh is the largest city of the Appalachian region, which is one of the poorest areas of the US, and consequently a region with very poor health indicators, including oral health indicators (Anjomshoaa, Cooper, and Vieira 2009). The phenotyping scheme used in our study takes into account ages and distribution of caries experience in the study participants. Individuals with very severe caries experience (DMFT higher than 10 by 20 years of age) demonstrated an association with a genetic variant in *RPTOR*. We have previously tested modifying the cut-off thresholds of those definitions and shown that there are no dramatic differences when the threshold is moved slightly (DMFT cut-off 9 in comparison to 10 or 11 (Deeley et al. 2008; Shimizu et al. 2013), but the limitation continues to be that we lose statistical power when trying to make more distinct groups eliminating intermediate values (comparing caries free with individuals with DMFT 10 or higher).

This is the first study that has provided evidence for association between a gene in the *mTOR* pathway and caries. *RPTOR*, particularly associated with dental caries in this study, regulates cell growth in response to nutrient and insulin levels (Foster et al. 2010). This information may turn out to be relevant for further cancer studies. We found that periodontal disease and osteoporosis were associated with SNPs in *IRE1* with allele A of rs16947425 increasing the risk

of osteoporosis almost 3-fold (p=0.00021, OR = 2.71, 95% C.I. 1.37 – 5.35). This result is remarkable, *IRE1* is involved in the development of secretory cells and organs (Reimold et al. 2000) as well as osteoclastogenesis (Tohmonda et al. 2015), suggesting that *IRE1* deficiency may induce osteopenia/osteoporosis with a slow bone turnover. However, these results should be taken cautiously particularly for osteoporosis, due to our study sample size of only twenty-two cases, it is difficult to estimate true odds ratios.

Recent evidence indicates that the inhibitory effects of *TSC1/TSC2* is mediated through *TSC2* inactivation of *RHEB* and it has been postulated that *TSC1/TSC2* complex inhibits *mTOR* signaling, that pathway is a central regulator of proliferation and cellular growth. Without this functional signaling, cells at the inflammatory sites cannot regenerate, and consequently there will be periodontal tissue destruction or higher predisposition for pulp inflammation even under slow progressing deep caries lesions in dentin. This process will be aggravated by swollen gums and accumulation of plaque.

In this present study, we have done a combined analysis of three phenotypes with the intention of finding a pleiotropic effect of the genotyped variants in the studied phenotypes. Previous studies looking at genetic variants were inconclusive in evidencing an association between caries and periodontitis; none of the gene variants that showed association with periodontitis had been associated with caries before (Nibali et al. 2017). In our study, both rs2374261 and rs1109089 markers in *RHEB* showed associations under the dominant model with individuals that had concomitant caries and periodontitis. This approach might be efficient in finding pleiotropic genes associated with oral phenotypes and help identify individuals with poor oral health outcomes and prognosis. We believe that sophisticating phenotype descriptions (Vieira 2018) and looking for patterns of disease affection (Koruyucu et al. 2018; Weber et al. 2018) based

on common underlying mechanisms (i.e. inflammation) are more promising approaches for identifying genes contributing to poor oral health outcomes than genome-wide association studies that use crude phenotypical descriptions such as “caries-free” versus ‘caries-affected”.

2.5 ACKNOWLEDGEMENTS

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3.0 PERFORMING AN ORAL PHENOME-WIDE SCAN IN CANCER DIAGNOSED INDIVIDUALS

3.1 FOREWORD

This chapter is adapted from a previously published manuscript in the Scientific Reports Journal. Mariana Bezamat et al. 2020. Phenome-Wide Scan Finds Potential Orofacial Risk Markers for Cancer. Scientific Reports.

3.2 SUBJECTS AND METHODS

Data from the Dental Registry and DNA Repository project available at the University of Pittsburgh were again used in this aim. All methods were performed in accordance with the guidelines and regulations. When data were collected, approximately 6,100 unrelated individuals who provided written informed consent were available (Vieira, Hilands, and Braun 2015; Vieira et al. 2017). Biospecimens were linked to patients' complete electronic health record (EHR) data (available on REDCap system), thus permitting analysis of associations between genetic variation obtained from DNA extracted from the specimens and dental and medical conditions. All data were deidentified, and biospecimens were linked to EHRs using a unique study number rather than personal identifying information. Complete medical and dental records, radiographs, oral photographs, and information about possible risk factors for cancer and other chronic conditions

were available, under specific codes created for the project. From the study database, a total of 350 individuals who have been diagnosed with cancer were first selected for the study. Then, a comparison group comprised of individuals who have never received a cancer diagnosis and were matched to the 350 patients in the experimental group by age, ethnicity, and sex reaching a 1:4 ratio was selected. Table 4 shows the distribution of the study sample and Figure 2 describes the overall study design.

Table 4. Study sample characteristics.

	Individuals with a Diagnosis of Cancer (n=350)		**Matched Individuals without a Diagnosis of Cancer** (n=1,321)	
Age in years (mean, range)	60.9	(13-91)	60.6	(13-97)
Sex (n, %)				
Female	187	(53.43%)	719	(54.43%)
Male	163	(46.57%)	602	(45.57%)
Self-reported Ethnicity (n, %)				
White	265	(75.71%)	1,042	(78.88%)
Black	75	(21.43%)	266	(20.14%)
Asian	2	(0.57%)	7	(0.53%)
Hispanic	3	(0.86%)	6	(0.45%)
Other	5	(1.43%)	0	(0.00%)

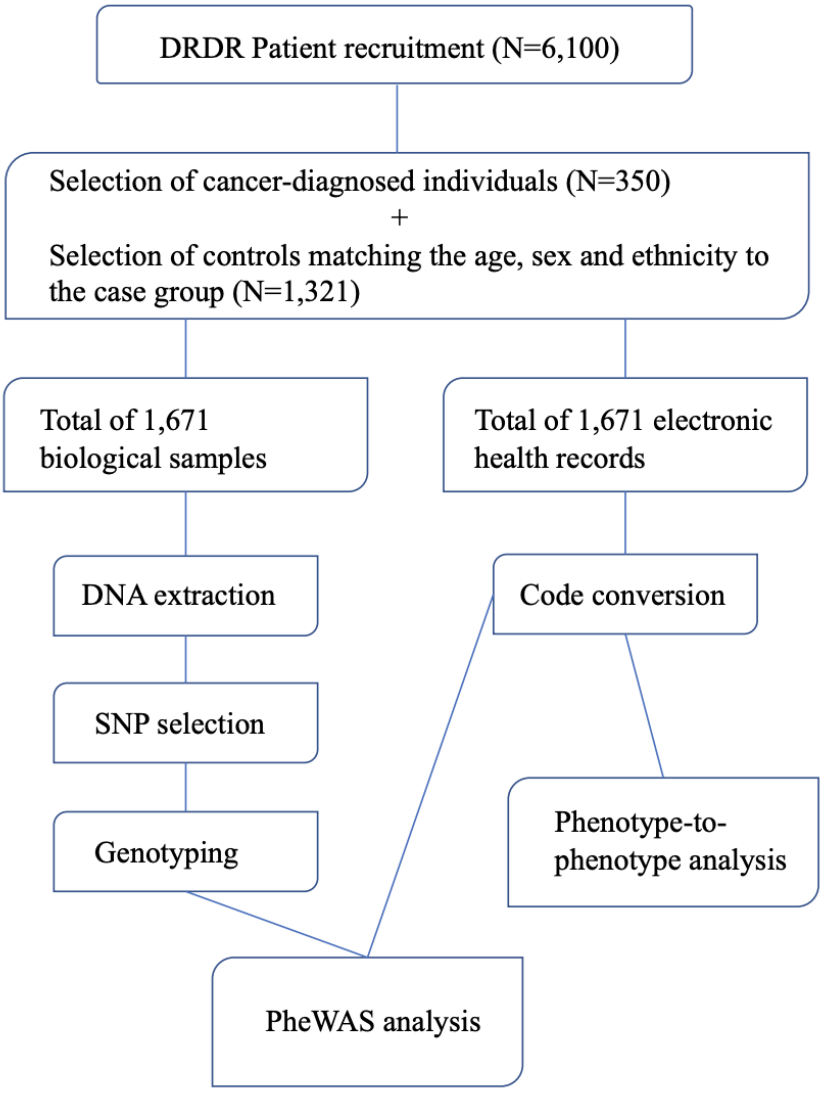


Figure 2. Overall study design.

The types of cancer in the study population are described by sex in Table 5. Phenotypes examined in this study included dental caries, diseases of the dental pulp and periapical tissues, dental abscess, diseases of the jaw, missing teeth or edentulism, acute periodontitis, chronic periodontitis, disorders of tooth development or eruption, tooth fracture, sleep related movement disorders (e.g., bruxism), diseases of salivary glands, malocclusion, stomatitis, mucositis,

erythema, lingual varicose veins, diseases of the tongue, temporomandibular joint disorder, hemangioma, lymphadenitis, candidiasis, thyroid disorders, and lacrimal gland disorders.

Table 5. Types of cancers in the study sample by sex.

Males		**Females**	
Cancer type	**# Cases**	**Cancer type**	**# Cases**
Prostate	38	Breast	56
Skin	35	Skin	29
Lymphoma	12	Cervix	19
Kidney	10	Colon/rectal	17
Rectal	9	Thyroid	12
Liver	6	Ovarian	7
Testicular	6	Leukemia	6
Throat	5	Lung	6
Lung	4	Uterine	5
Bladder	4	Oral	2
Thyroid	3	Myeloma	2
Oral	3	Head	2
Leukemia	3	Bladder	2
Parotid gland	2	Endometrial	2
Esophagus	2	Throat	1
Brain	2	Liver	1
Adenocarcinoma	2	Adenocarcinoma	1
Other	16	Other	12

3.2.1 **Phenotype-to-phenotype analysis**

Individuals diagnosed with cancer were matched with individuals without cancer according to their age, ethnicity and sex, since these variables associate with the onset or frequency of many outcomes we selected to study. Then, a chi-square test (alpha = 0.05) was performed to ascertain if particular dental outcomes preferentially associated with each other. The frequency of the most common head and neck conditions in the group of individuals who received a diagnosis of cancer was compared with the group of individuals who were not diagnosed with cancer. We tested phenotypes such as the presence of diseases of pulp and periapical tissues, periodontitis (acute or chronic), tooth loss/edentulism, dental caries and anomalies of jaw size/symmetry.

Since we had medical information available to us, we further tested if additional comorbidities associated with cancer in our study population as well. The self-reported comorbidities tested were epilepsy, stroke, asthma, tuberculosis, anemia, hepatitis, liver disease, irregular heartbeat, rheumatic fever, heart murmur, heart surgery, diabetes, HIV and kidney disease. The analysis included two-by-two tables and chi-square tests with an alpha set to 0.05.

3.2.2 **Genomic polymorphisms**

We have tested SNPs based on the data obtained in section 1, where we tested 27 markers in eight genes of two pathways involved with protein synthesis and cell homeostasis, and five oral phenotypes (Bezamat et al. 2019). Results showed that the SNPs rs2374261 (*RHEB*), rs1109089 (*RHEB*), rs4396582 (*RPTOR*) and rs196929 (*IRE1*) associated with three oral phenotypes (dental caries, periodontitis, and periapical lesions). Those SNPs are present in pathways involved in cell proliferation, differentiation, protein synthesis and inflammation, and may contribute to cancer risk as well. We also tested variation marking *AXIN2* (rs2240308 and rs11867417), based on its

association with cancer in different populations as well as craniofacial phenotypes such as cleft lip and palate and tooth agenesis, reported in previous studies (Lammi et al. 2004; Callahan et al. 2009; Ma et al. 2014; D. Liu et al. 2014; Z. Wu et al. 2015; X. Liu et al. 2016; Y. Han et al. 2014; Letra et al. 2009; S.S. Wang et al. 2006). Table 6 lists the genes, the selected SNPs and their minor allele frequencies (MAF).

Table 6. Selected SNPs and their minor allele frequencies (MAF).

Gene	SNP	MAF
IRE1	rs196929	T=0.4046
RHEB	rs2374261	T=0.3900
	rs1109089	T=0.3958
AXIN2	rs2240308	A=0.3377
	rs11867417	C=0.4675
RPTOR	rs4396582	G=0.4113

3.2.3 **DNA extraction**

Genomic DNA was extracted from salivary samples of the 1,671 individuals using established protocols (Aidar and Line 2007). In order to run the polymerase chain reaction (PCR) using the selected SNPs, DNA samples were diluted in Tris- EDTA (TE) buffer to a concentration of 2 ng/µl. Then, a volume of 1.0 µl was transferred to PCR plates and 2.0 µl of reaction mix containing master mix, water and the SNP of interest was added to each well of the 384 well plate. Reactions were carried out using TaqMan chemistry in volumes of 3.0 µl in an ABI PRISM Sequence Detection System 7900, software version 1.7 (Applied Biosystems, Foster City, CA, USA). Genotypes were generated blindly to clinical diagnosis status.

3.2.4 **Genotypic analysis**

Association analyses were performed comparing genotypes and allele frequencies between individuals diagnosed with cancer and the unaffected group for each SNP as implemented in PLINK (Purcell et al. 2007). Different models are available, the allelic model compared the frequencies of each allele in each group (D x d); assuming that D is the minor allele and d is the major allele. The genotypic model is an additive two degree of freedom model and compared the frequencies of each genotype in the groups (DD x Dd x dd), the dominant model compared the two copies of the common alleles frequency versus the other combinations (dd x DD + Dd), and the recessive model compared the two copies of the rare alleles frequency versus the other combinations (DD x Dd + dd). P-values below 0.008 (0.05/6; the denominator is the number of genetic markers tested) were considered statistically significant.

3.2.5 **Code conversion**

As the Dental Registry and DNA Repository project uses internal specific codes that better describe dental conditions instead of the more general International Classification of Diseases - Ninth Revision (ICD-9), and the PheWAS package in R studio only reads ICD-9 codes or "Phecodes", we included as part of our strategic approach the conversion of our internal codes into "Phecodes" to be able to run the PheWAS analysis. Treatments and phenotypes were recoded and identified by "Phecodes" and each tooth might have more than one code according to the number of different phenotypes in the tooth. The information of treatments previously provided is important to help us determine whether a tooth had previous dental caries, successive restorations' failures or unsuccessful treatments leading to extractions for example. The way the program is

written, the use of universal codes or “Phecodes” is required for the analytic software to perform the analysis of these data. The raw data were gathered from the Dental Registry and DNA Repository project through REDCap (Research Electronic Data Capture) hosted at the University of Pittsburgh (P.A. Harris et al. 2009). Data were exported in the form of an Excel file, which was converted to a Comma Separated Variable file (.CSV). The.CSV file was then read and processed by a script that converted all relevant codes from project’s internal form to their Phecode form. A program was written in JavaScript to read the .CSV file. A list of valid conversions was manually created by us (Appendix Table 13) according to the codes we have available in our project and a phecode catalog map that can be found at www.phewascatalog.org - the codes can be identified by either typing the correspondent ICD9 code or the phenotype of interest. The list also in the .CSV form, was entered into the script, and the program replaced all occurrences of relevant raw codes to their Phecode form and a “true or false” file was manually created for each of the phenotypes in a particular individual. This final file was then uploaded into R to be used in the PheWAS analysis.

3.2.6 **PheWAS statistical methods and power calculation**

The R software has a PheWAS package that generates perfect matches between affected individuals and their comparators for each individual set of phenotypes. Each phenotype includes an optional set of exclusion phenotypes for similar diagnoses to more accurately identify true controls. This step prevents patients with similar diseases from being marked as a control during the statistical analysis (Carroll, Bastarache, and Denny 2014). The current PheWAS map and PheWAS script written in R is available at http://phewascatalog.org (Carroll, Bastarache, and Denny 2014). The standard PheWAS statistical test is a logistic regression that calculates odds ratios, p-values, and includes Bonferroni correction to account for multiple testing. We used the

additive genomic model, assuming that each allele contributes a fixed amount of risk that is additive. We incorporated sex and ethnicity as covariates in the logistic regression analysis in order to adjust for potential confounding effects.

According to a simulation study that investigated power estimates in PheWAS, a sample size of 200 cases or more achieves 80% statistical power to identify associations for common variants. In addition, a sample size of 1,000 or more individuals performed best in the simulations (Verma et al. 2018). Our total sample consists of 1,671 individuals, 350 diagnosed with cancer and 1,321 non-affected by cancer, which gives an approximate 1:4 case-control ratio. Considering sample size, case-control ratio, and minor allele frequencies of our SNPs **(**Table 6**)**, the analysis of the cohort defined by having cancer will have a power of 100% to detect possible associations with α at 0.00025.

3.3 RESULTS

We performed a phenotype-to-phenotype analysis, in which we compared the frequency of the most common orofacial conditions between cancer diagnosed individuals and a group of patients that were not diagnosed with cancer. As expected, the frequency of some oral diseases is high in the individuals participating in the Dental Registry and DNA Repository project. For example, among the 350 patients who reported having cancer, 84 have been diagnosed with periodontitis and 134 have been diagnosed with diseases of pulp and periapical tissues, versus 304 and 490 individuals out of 1,321 in the group without cancer for the same respective treatments. The most frequent condition was tooth loss/edentulism with 327 individuals being affected in the cancer diagnosed group versus 1147 in the group without cancer. We used these frequencies to

calculate power, considering the incidence of tooth loss/edentulism in the affected group as 93%, and in the unaffected as 87%. Our total sample of 1,671 individuals gives 91% power to detect associations with an alpha of 0.05. When less frequent phenotypes or more similar incidence percentages within comparison groups are considered, the power decreases substantially. All additional power calculations for each individual condition are represented in Table 7.

Table 7. Oral conditions present in patients diagnosed with and without cancer, chi-square results (P-value below the significance threshold of 0.05 is marked in bold) and statistical power.

Phenotype	Diagnosed with cancer (N=350)	Non-diagnosed with cancer (N=1,321)	P-value	Odds Ratio	Statistical Power
Diseases of pulp and periapical tissues	134	490	0.68	1.05	5.4%
Periodontitis (acute or chronic)	84	304	0.69	1.05	6%
Tooth loss/edentulism	327	1,147	**0.0006**	2.15	91%
Dental caries	237	843	0.17	1.18	28.2%
Anomalies of jaw size/symmetry	5	22	0.75	0.85	3.9%

The results showed that having tooth loss makes one more likely to have been diagnosed with cancer [327 out of 350 have tooth loss in the affected group and 1,147 out of 1,321 in the unaffected group ($p = 0.0006$, $OR = 2.15$, 95% C.I. 1.37–3.38)]. All the remaining orofacial phenotypes tested did not show any statistical difference between the two compared groups **(**Table 7**)**.

Our additional chi-square analysis between cancer and the presence of comorbidities identified several associations such as with hepatitis (p = 0.0007), asthma (p = 0.01), heart murmur (p = 0.001), diabetes (p = 0.01), kidney disease (p = 0.02) and anemia (p = 0.01) with the cancer group. In the genotypic analysis an association between the group of individuals affected with different cancers and *IRE1* rs196929 was identified in the genotypic (2df) model (Table 8). The heterozygous genotype (TC) was more frequent than the homozygous genotypes in the individuals diagnosed with cancer whereas the homozygous for allele 2 genotype (CC) was more frequent in the unaffected matched controls.

Table 8. Results from the genotypic analysis of patients diagnosed with cancer (bold indicates statistically significant p-values under the threshold 0.008). Assuming that D is the minor allele and d is the major allele, the allelic model compares the frequencies of each allele in each group (D x d), the genotypic (GENO) model is an additive two degree of freedom model that compares the frequencies of each genotype in the groups (DD x Dd x dd), the dominant (DOM) model compares the two copies of the common alleles frequency versus the other combinations (dd x DD + Dd), and the recessive (REC) model compares the two copies of the rare alleles frequency versus the other combinations (DD x Dd + dd). Chromossome (CHR), Allele 1 and 2 (A1, A2), Chi-square value (X^2).

CHR	SNP	A1	A2	TEST	Affected	Unaffected	X^2	Degrees of Freedom	P-value
7	rs1109089	T	C	GENO	66/153/104	278/524/421	2.172	2	0.3375
7	rs1109089	T	C	ALLELIC	285/361	1080/1366	0.0002697	1	0.9869
7	rs1109089	T	C	DOM	219/104	802/421	0.5643	1	0.4526
7	rs1109089	T	C	REC	66/257	278/945	0.7797	1	0.3772
7	rs2374261	T	C	GENO	62/146/102	259/500/404	1.759	2	0.415
7	rs2374261	T	C	ALLELIC	270/350	1018/1308	0.009432	1	0.9226
7	rs2374261	T	C	DOM	208/102	759/404	0.3653	1	0.5456
7	rs2374261	T	C	REC	62/248	259/904	0.74	1	0.3897

17	rs196929	T	C	GENO	32/153/123	152/472/569	10.31	2	**0.0058**
17	rs196929	T	C	ALLELIC	217/399	776/1610	1.617	1	0.2035
17	rs196929	T	C	DOM	185/123	624/569	5.932	1	0.01487
17	rs196929	T	C	REC	32/276	152/1041	1.258	1	0.262
17	rs4396582	G	A	GENO	76/156/93	272/576/335	0.04994	2	0.9753
17	rs4396582	G	A	ALLELIC	308/342	1120/1246	0.000458	1	0.9829
17	rs4396582	G	A	DOM	232/93	848/335	0.0111	1	0.9161
17	rs4396582	G	A	REC	76/249	272/911	0.0221	1	0.8818
17	rs11867417	T	C	GENO	48/111/85	160/388/335	0.8472	2	0.6547
17	rs11867417	T	C	ALLELIC	207/281	708/1058	0.8588	1	0.3541
17	rs11867417	T	C	DOM	159/85	548/335	0.7872	1	0.3749
17	rs11867417	T	C	REC	48/196	160/723	0.306	1	0.5801
17	rs2240308	A	G	GENO	46/134/106	230/455/403	4.22	2	0.1212
17	rs2240308	A	G	ALLELIC	226/346	915/1261	1.203	1	0.2728
17	rs2240308	A	G	DOM	180/106	685/403	4.914e-005	1	0.9944
17	rs2240308	A	G	REC	46/240	30/858	3.606	1	0.05756

The PheWAS analysis **(**Table 9**)** revealed several suggestive associations between craniofacial phenotypes and the SNPs tested. However, there were no significant associations after Bonferroni correction. A trend for association was found between *AXIN2* rs11867417 minor allele and the presence of glossitis (p = 7.80E-04, OR = 2.48, 95% C.I. 1.49–4.36). Figure 3 illustrates the most substantial results in the total sample. We set a threshold value of p = 0.002 (horizontal red line) in all Manhattan plots in order to facilitate visualization of trends for association. The horizontal blue line represents the p = 0.05 threshold, phenotypes found below the blue line are not annotated in the plots to avoid noise. The triangle tip direction represents the odds ratio direction of each association. In order to identify whether these associations were preferentially linked to the individuals with a cancer condition in our population, we ran PheWAS in both cancer-affected **(**Figure 4 and Table 10**)** and unaffected samples separately (Table 11). Table 10 shows the results obtained in the cancer-affected sample and table 11 shows the results obtained after

analysis of the cancer-unaffected sample. When analyzing the cancer affected group separately, tooth loss/edentulism and leukoplakia of oral mucosa are within the phenotypes that showed trends for association with a number of different SNPs. Interestingly, when the comparison group was analyzed, no significant associations with these phenotypes were identified, leading us to suggest that they are possibly unique to the cancer affected sample.

Table 9. PheWAS results in the total sample. Logistic regression using the additive genomic model was performed and the table shows the nominal results (p values between 0.00025 and 0.05). Significant results were not identified.

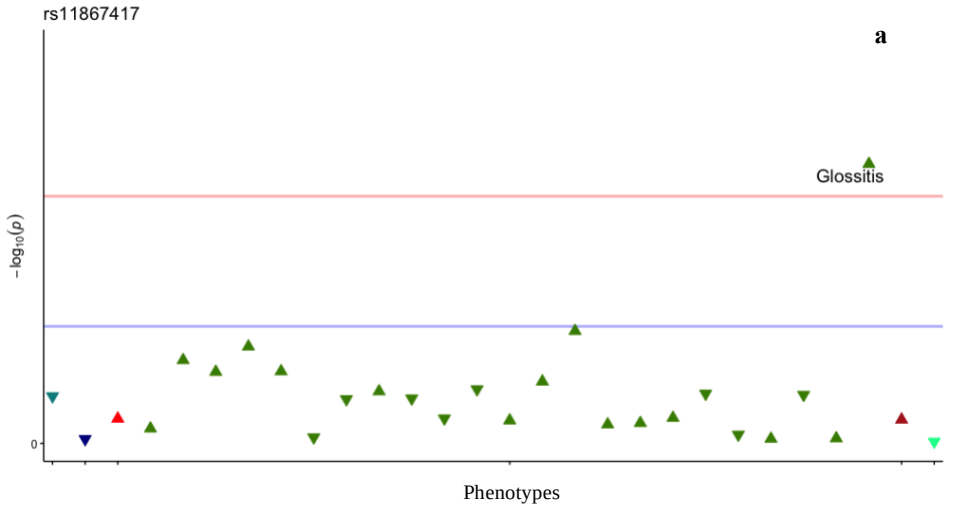
Phecode	Description	SNP_Allele	Lower	Upper	Odds Ratio	P value	Affected by the disease described (%)	Non-affected by the disease described (%)	Allele frequency
525	Tooth fracture	rs2374261_T	1.187	1.849	1.480	5.08E-04	181 (12%)	1289 (88%)	0.43
529.1	Glossitis	rs11867417_C	1.498	4.368	2.486	7.80E-04	39 (3%)	1088 (97%)	0.59
525	Tooth fracture	rs1109089_T	1.146	1.772	1.424	1.43E-03	186 (12%)	1356 (88%)	0.44
528.6	Leukoplakia of oral mucosa	rs2240308_A	0.676	0.942	0.799	7.97E-03	391 (28%)	983 (72%)	0.41
526.4	Temporomandibular joint disorder	rs2374261_T	1.045	1.409	1.213	1.08E-02	555 (38%)	915 (62%)	0.43
523.1	Gingivitis	rs2240308_A	0.703	0.974	0.828	2.39E-02	406 (30%)	968 (70%)	0.41
526.3	Anomalies of jaw size/symmetry	rs1109089_T	0.207	0.880	0.446	2.69E-02	20 (1%)	1522 (99%)	0.44
523.32	Chronic periodontitis	rs2240308_A	0.645	0.980	0.796	3.33E-02	211 (15%)	1163 (85%)	0.58
520	Disorders of tooth development	rs1109089_T	1.021	2.149	1.477	3.89E-02	58 (3%)	1484 (97%)	0.44
528.11	Stomatitis and mucositis	rs4396582_G	1.015	1.949	1.403	4.07E-02	78 (5%)	1427 (95%)	0.47

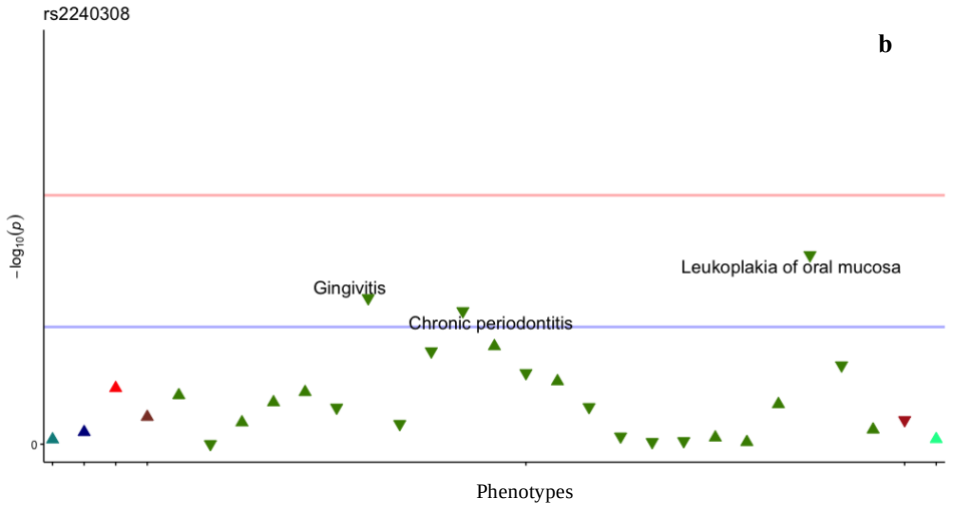
Table 10. PheWAS results in the patients that had cancer. Logistic regression using the additive genomic model was performed and the table shows the nominal results (p values between 0.00025 and 0.05). Significant results were not identified.

Phecode	Description	SNP_Allele	Lower	Upper	Odds Ratio	P value	Affected by the disease described (%)	Non-affected by the disease described (%)	Allele frequency
523.3	Periodontitis (acute or chronic)	rs1109089_T	0.384	0.841	0.572	0.0052	80 (25%)	240 (75%)	0.44
		rs2374261_T	0.383	0.858	0.578	0.0076	75 (24%)	239 (76%)	0.43
523.1	Gingivitis	rs11867417_C	0.413	0.927	0.623	0.0213	70 (29%)	169 (71%)	0.57
		rs4396582_G	0.483	0.971	0.688	0.0355	106 (32%)	220 (68%)	0.46
529	Diseases of the tongue	rs2374261_T	0.489	0.951	0.685	0.0258	142 (45%)	172 (55%)	0.43
525.1	Tooth loss/ edentulism	rs2240308_A	1.134	4.979	2.269	0.0281	263 (92%)	22 (8%)	0.41
		rs11867417_C	1.108	4.016	2.066	0.0258	217 (91%)	22 (9%)	0.57
528.6	Leukoplakia of oral mucosa	rs2240308_A	0.448	0.945	0.655	0.0257	86 (30%)	199 (70%)	0.41
		rs2374261_T	1.029	2.096	1.464	0.0348	95 (30%)	219 (70%)	0.43

Table 11. PheWAS results in the patients that did not have cancer. Logistic regression using the additive genomic model was performed and the table shows the nominal results (p values between 0.00025 and 0.05). Significant results were not identified.

Phecode	Description	SNP_Allele	Lower	Upper	Odds Ratio	P value	Affected by the disease described (%)	Non-affected by the disease described (%)	Allele frequency
525	Tooth fracture	rs2374261_T	1.140	1.884	1.464	2.89E-03	137 (12%)	1019 (88%)	0.44
		rs1109089_T	1.130	1.850	1.444	3.37E-03	141 (12%)	1081 (88%)	0.44
		rs2240308_A	0.576	0.983	0.755	3.94E-02	122 (11%)	967 (89%)	0.42
523.32	Chronic Periodontitis	rs2374261_T	1.067	1.675	1.336	1.14E-02	178 (15%)	978 (85%)	0.44
		rs1109089_T	1.020	1.572	1.266	3.20E-02	193 (16%)	1029 (84%)	0.44
529.1	Glossitis	rs11867417_C	1.211	3.914	2.113	1.16E-02	31 (3%)	857 (97%)	0.60
523.1	Gingivitis	rs2240308_A	0.659	0.949	0.792	1.21E-02	320 (29%)	769 (71%)	0.42


rs11867417
a
Glossitis
$-\log_{10}(p)$
0
Phenotypes


rs2240308
b
Leukoplakia of oral mucosa
Gingivitis
Chronic periodontitis
$-\log_{10}(p)$
0
Phenotypes

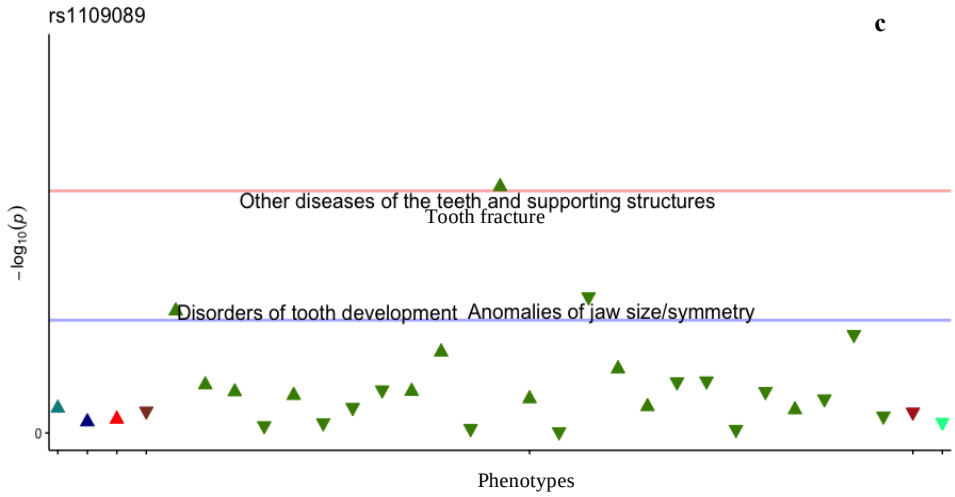
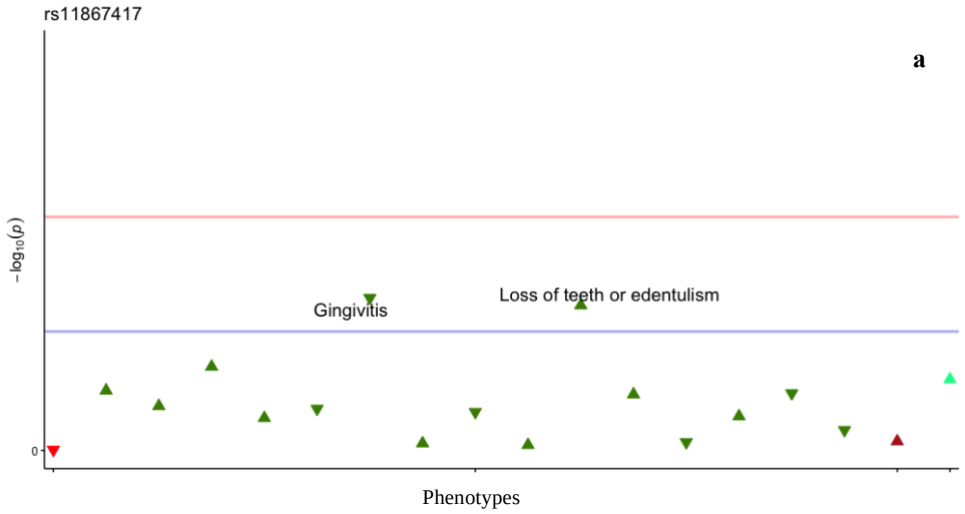
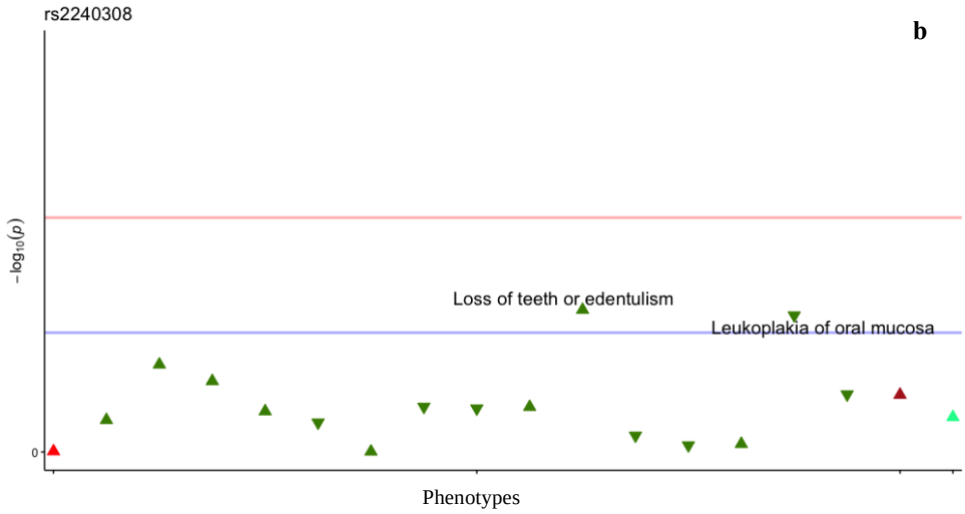

rs1109089
c
Other diseases of the teeth and supporting structures
Tooth fracture
Disorders of tooth development
Anomalies of jaw size/symmetry
$-\log_{10}(p)$
0
Phenotypes

Figure 3. Plot representing the phenome-wide association analysis in the total sample. The horizontal red line indicates the threshold of p=0.002; the horizontal blue line indicates the threshold of p=0.05, phenotypes found below the blue line (p>0.05 – not associated) are not annotated in the plots to avoid noise. The triangle tip direction represents the odds ratio direction of each association, upward triangles indicate OR ≥ 1; downward triangles indicate a protective effect (OR < 1.0); different triangle colors indicate different disease groups (from left to right – dark green=neoplasms, dark blue=neurological system, bright red=circulatory system, brown=respiratory, green=digestive, dark red=dermatologic and light blue=congenital anomalies). (a) ***AXIN2*** **- rs11867417 and its association with glossitis (p<0.002). (b)** ***AXIN2*** **- rs2240308 and its protective effect towards having gingivitis, chronic periodontitis, and leukoplakia of the oral mucosa (p<0.05). (c)** ***RHEB*** **- rs1109089 and its association with both disorders of tooth development (p<0.05), and tooth fracture (p<0.002), and its protective effect towards anomalies of jaw size/ symmetry (p<0.05).**


rs11867417
a
$-\log_{10}(p)$
Gingivitis
Loss of teeth or edentulism
0
Phenotypes


rs2240308
b
$-\log_{10}(p)$
Loss of teeth or edentulism
Leukoplakia of oral mucosa
0
Phenotypes

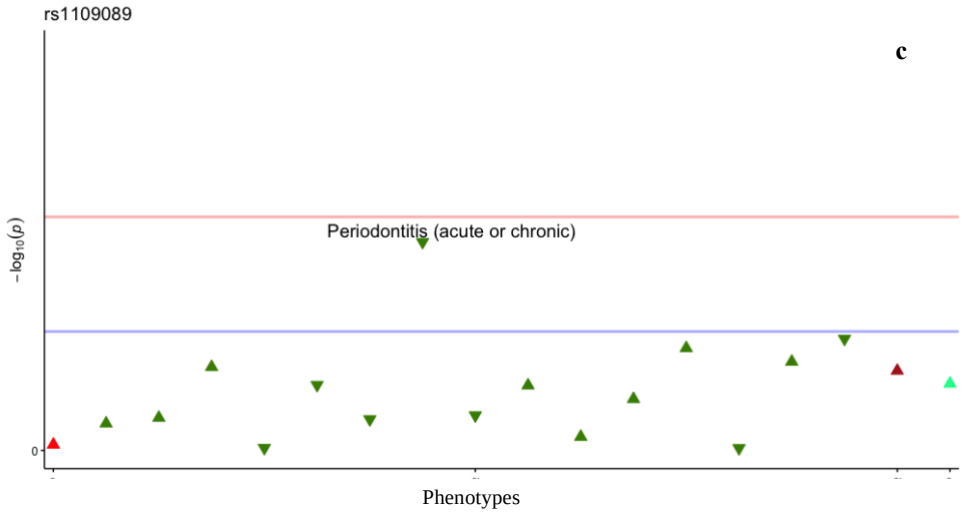

rs1109089
c
$-\log_{10}(p)$
Periodontitis (acute or chronic)
0
Phenotypes

Figure 4. Plot representing the phenome-wide association analysis in the cancer-affected sample. The horizontal red line indicates the threshold of p=0.002; the horizontal blue line indicates the threshold of p=0.05, phenotypes found below the blue line (p>0.05 – not associated) are not annotated in the plots to avoid noise. The triangle tip direction represents the odds ratio direction of each association, upward triangles indicate OR ≥ 1; downward triangles indicate a protective effect (OR < 1.0); different triangle colors indicate different disease groups (from left to right – light red=circulatory system, green=digestive, dark red=dermatologic and light blue=congenital anomalies). (a) *AXIN2* - rs11867417 and its association with loss of teeth/edentulism, and its protective effect towards gingivitis (p<0.05). (b) *AXIN2* - rs2240308 and its association with loss of teeth/edentulism and its protective effect against leukoplakia of the oral mucosa (p<0.05). (c) *RHEB* - rs1109089 and its protective effect against periodontitis (p<0.05).

3.4 DISCUSSION

Here we report an analysis of a cohort enriched with individuals diagnosed with cancer using PheWAS in an attempt to identify oral health outcomes and genetic variants that may be indicators of cancer risk. Nominal associations were found when the cancer-affected patients were analyzed separately. For both SNPs in *RHEB*, the less frequent alleles appeared to be protective of having periodontitis in the cancer diagnosed individuals, and having anomalies of jaw size/ symmetry in the total sample. Both *RHEB* and *RPTOR* genes are present in the signaling pathway known as the mammalian target of rapamycin (*mTOR*). The *mTOR* signaling is a master regulator of protein synthesis, *RHEB* (Ras homolog enriched in brain) is a positive regulator of *mTOR* and is located in the center of the signaling pathway (Sciarretta et al. 2018). *RPTOR* (the Regulatory Associated Protein of mTOR) regulates cell growth in response to nutrient and insulin levels

(Sabatini 2017). Activation of *mTOR* promotes tumor growth and metastasis (Hua et al. 2019). *Rptor* knockout mice display facial growth deficiency, including mandible (Schachter et al. 1985), which is consistent with our finding.

Unique associations were also identified for a number of other markers in the cancer-affected group; two markers in *AXIN2* and loss of teeth/edentulism and a marker in *RHEB* and leukoplakia of the oral mucosa showed associations. *AXIN2* is a component of Wnt signaling and is expressed in the dental mesenchyme, dental papilla and enamel knot (X. Wu et al. 2017). The *AXIN2* rs2240308 polymorphism results in an amino acid change from a proline to a serine (Pro50Ser) located at exon 1 148 of this gene and has been suggested to influence AXIN expression (Z. Wu et al. 2015). This SNP has also been suggested as a risk marker for colorectal cancer predisposition (Otero et. Al 2019). Authors of another article proposed the mechanism causing colorectal cancer being mutations in *AXIN2* with mismatch repair by activating beta-catenin/ TCF signaling (Liu et al. 2000). A recent study reported that Axin2 cells maintain expression in cementoblasts in adult mice. Their results showed that cells in mice's periodontal ligament receiving Wnt signals differentiated into cementoblasts during homeostasis (Zhao et al. 2021), and another study concluded that Wtn signaling is essential for new cementum deposition and lesion repair (Turkkahraman et al. 2021). It might be plausible to suggest that change in AXIN expression could be disrupting homeostasis and cementoblast replenishment, leading to higher susceptibility to tooth loss due to periodontitis in the cancer-affected individuals in a similar way that it increases predisposition to colorectal cancer. More specifically, increased levels of b catenin in the cell caused by an impaired degradation complex and increased canonical Wtn signaling could be affecting self-renewal and periodontal ligament stem cells differentiation as a mechanism proposed for stem cells before (Yang et al. 2015). Cementoblast differentiation is not fully understood

(Nemoto et al. 2015) but altered differentiation in those cells could be impacting proper cellular cementum deposition. A study showed an absence of transcripts of bone sialoprotein in follicle mesenchyme as a composition change observed in disrupted cementogenesis (Zhang et al. 2013). This disruption in cementum structure could be affecting the entire periodontium complex, increasing susceptibility to bacterial apposition, growth and consequently inflammation. Tissue remodeling and bone resorption will then occur, making one more susceptible to tooth loss. This mechanism is supported by the opposite results found in the group of patients who had never received a cancer diagnosis. This group presented an association between the same SNP (*AXIN2* rs2240308) and lower risk of developing gingivitis which is a milder form of gum disease that can evolve to periodontitis.

We suggest that the association between *RHEB* and leukoplakia, which is associated with increased risk of oral cancer, has to do with inflammation and regulation of *RHEB/mTOR* signaling. A study performed in mice, showed that loss of *Rheb* in macrophages repressed inflammation, whereas overexpression of this same gene increased inflammation (Zhang et al. 2019). In our study, most of the glossitis affected individuals presented geographic tongue and disruption in inflammatory response pathways might be the most explainable mechanism for the association between *AXIN2* rs11867417 SNP and glossitis as well.

Our results suggest a role of *AXIN2* in tooth loss. Previous studies have shown an association between *AXIN2* and tooth agenesis (Callahan et al. 2009; Mostowska, Biedziak, and Jagodzinski 2006) and in our study we cannot discard the possibility of a missing tooth due to agenesis being reported as tooth loss if the patient had that missing tooth prior to the start of the treatment in the dental school. However, that possibility is low due to the prevalence of tooth agenesis varying from 2.2 to 10.1% (Bozga, Stanciu, and Manuc 2014).

No significant associations were found when analyzing the cancer-affected group in separate (after Bonferroni correction). This may be due to the reduced power of the smaller sample size of the cancer-affected group. Nevertheless, the p-values below 0.00025 set after Bonferroni correction may be too strict especially if we consider that some of the oral phenotypes might be related. Examples of these include most cases of periapical lesions which are caused by dental caries, or gingivitis that can evolve to periodontitis. This strict multiple testing correction may lead to missing true biological signals (Vieira et al. 2008).

The phenotype-to-phenotype analysis showed an association between having had tooth loss and having been diagnosed with cancer, consistent with the results obtained in the PheWAS analysis. Since not only tooth loss/edentulism but also leukoplakia of oral mucosa are examples of phenotypes that showed associated in individuals diagnosed with cancers, different types of cancers could be better defined to confirm if these oral health outcomes associate. Similarly, when genetic variation was analyzed as potential risk markers in the total sample, some of the results after correction for multiple testing suggest that the risk alleles are not overrepresented among individuals affected by cancer, making it difficult to use those specific phenotypes as markers of risk.

This is the first time that a phenome-wide study has been performed using a dental database and we demonstrated the applicability of the technique to the dental field and dental researchers for future studies. However, a few limitations were experienced. We were not able to differentiate between losing one tooth, including third molars, and losing all teeth (edentulism). Refining these and other phenotypes in future studies, is an approach that will help clarify if edentulism, which is an extreme outcome, is a risk marker for cancer. A previous meta-analysis performed with the intention of seeking for association between oral health and colorectal cancer included studies that

took into account the number of teeth lost. Subjects with no teeth lost, 1-8 or 9-20 teeth lost were compared with subjects who had more than 20 teeth lost due to dental caries and/or periodontitis. They concluded that there was a lack of evidence for association between oral health and colorectal cancer risk (Ren et al. 2016). Nonetheless, in their methodology, the number and reason for tooth loss was self-reported which constitutes a great limitation of the study since not always the patient remembers how many teeth he lost and what specific reason led to tooth extraction other than pain.

The second limitation we faced here is that the types of cancer present in our study sample are not representative of the most frequent cancers in the general population. Lung cancer, for example, is the second most common cancer, for both men and women. However, in our Dental Registry and DNA Repository project, only ten subjects (four males and six females) reported having lung cancer. The reason for this difference might be explained by the high mortality rate of lung cancer in patients. For a patient to participate in the Dental Registry and DNA Repository project and report having had cancer, they either survived the disease or are undergoing treatment. Therefore, there is a higher probability that these individuals had a type of cancer with a low five-year survival rate and were not captured in our sample. Further, ideally, we would be able to replicate our work in another cohort, but our project is the only one in the world that includes over 40 specific oral phenotypes that were diagnosed by a careful dental exam. Dental phenotypes especially are typically omitted from such studies since they are not part of medical records.

Analyses were done taking into consideration sex and ethnicity. Females and males share a genome but differ in almost every phenotype (Cheng and Kirkpatrick 2017), including oral health outcomes such as dental caries (Deeley et al. 2008). We used self-reported ethnicity as an adjustment in the regression analysis, and we are aware that there are instances that some self-identified African Americans may have a high percentage of European ancestry, whereas some

self-identified European Americans have substantial admixture from African ancestry (Mersha and Abebe 2015). To mitigate the potential effect of population substructure, ancestry may be derived from genetic data. Our previous experience with the data from the Dental Registry and DNA Repository project suggests that there is good consistency between self-reported and genetically driven ethnicity definitions (Feng et al. 2014). Comparisons between estimates of genetic ancestry and self-reported ethnicity in African and European American populations from 1000 genomes project datasets showed that European ancestry estimations from genetic data was 97.6% for individuals that self-reported as Europeans, only 1.3% for individuals that self-reported as Africans, and 10.8% for individuals that self-reported as African Americans (Mersha and Abebe 2015). The analysis could also not account for known factors that modify oral health outcomes. We did not include a surrogate for socioeconomic status in the analysis, however the participants of our Dental Registry and DNA Repository project are for the most part, from lower socioeconomic status and have poor oral and overall health outcomes (Vieira, Hilands, and Braun 2015). We also could not include a measure for the potential consequence of cancer on the patient's oral health. Cancer treatment can be as devastating as the disease itself, with the aggravating factor that dentists can be perceived as less knowledgeable about cancer treatment-related oral concerns and therefore trusted less than oncologists (Taichman, Van Poznak, and Inglehart 2018; Epstein and Barasch 2018).

In summary, previously suggested associations in the studied genes were consistent with our findings and novel potential associations were identified. Tooth loss/edentulism was associated with two *AXIN2* SNPs in the cancer-affected sample, increasing up to 2.3 times the chances of losing teeth. The phenotype-to-phenotype analysis showed similar results, confirming that individuals diagnosed with cancer experience more tooth loss. This particular association could be

just the result of the cancer itself, since most of the cancer diagnosed patients have immunosuppression, which consequently may lead to tooth loss. However, one should consider that a particular phenotype that is the result of a person's cancer still may be more likely to be identified prior to the cancer itself being identified. Individuals with immune system disorders, such as Dubowitz or Down syndromes, show characteristic facies and dental abnormalities and higher incidence of leukemia/lymphoma (Joshi, Hamdan, and Fakhouri 2014).

This study implemented a novel strategy to identify cancer risk markers by combining electronic health records and genetics. Identification of individuals carrying craniofacial and genetic markers allow dentists to refer them for screenings/checkups more frequently. This conduct potentially increases the possibility of preventing cancers or diagnosing them at early stages when the treatment survival rates are higher.

3.5 ACKNOWLEDGEMENTS

The University of Pittsburgh Dental Registry and DNA Repository provided data and DNA samples for this study. Sincere thanks to Robert Carroll for his help with the PheWAS package and analyses, to Katherine Glickman and Benjamin Harrison for their help with genotyping and to Christopher Guirguis for his help with the code conversion.

4.0 **CONCLUSIONS AND FUTURE DIRECTIONS**

We first concluded that variation in both *mTOR* and ER stress genes showed to be associated with osteoporosis, and variation in *mTOR* genes were associated with periapical lesions and dental caries. Additionally, different associations in both pathways were detected when oral conditions were analyzed in combination (Bezamat et al. 2019). However, these combined-disease associations were not always more significant than the ones in the isolated-disease analysis as we hypothesized. We then, concluded that previously suggested associations in the studied genes were consistent with our findings and novel associations were identified. We confirmed that there is a range of orofacial phenotypes nominally associated with cancer both indirectly, such as tooth fracture, glossitis and temporomandibular joint disorder through cancer associated genes and directly such as tooth loss/edentulism through the phenotype-phenotype analysis (Bezamat et al. 2020). These orofacial phenotypes can potentially serve as cancer risk markers. The results showed tooth loss and edentulism associated with cancer in both a phenotype-to-phenotype analysis and phenotype-genotype analysis.

Our study is the first of its kind to conduct a PheWAS in cancer affected patients with the intention of finding both genetic and orofacial phenotypic markers for cancer experience. Future studies could include an increased sample of cancer affected individuals to consequently increase statistical power and detect significant associations. Collaborations with different dental schools and centers are warranted in order to include oral heath indicators that are measured by dental health professionals instead of the vastly used self-reported outcomes. Including a greater sample size will also allow for individualized analyses of different types of cancer, improving the possibility of early diagnosis. Another suggested future work could define the time at cancer

diagnosis regarding the appearance of each orofacial phenotype indicating if a specific trait could serve as a risk marker. This can be done by performing a prospective cohort study or even a retrospective study using the cohort we used here. The DRDR database allows for some longitudinal research in subjects who have been treated in our dental school for a long period of time. With that, we can jump back in time and identify available data regarding cancer diagnosis of those particular individuals. Additionally, the DRDR study includes a signed consent form with the possibility of future contact, which authorize investigators to call or email the subjects and obtain missing data. That can be done for those subjects that information regarding the time at cancer diagnosis are missing in the database.

Finally, a next step could involve the inclusion of many additional SNPs in candidate genes or even the conduction of a PheGWAS which combines both GWAS and PheWAS approaches utilizing the "many variants-many phenotypes" scenario. The PheGWAS technique might assist in detecting pleiotropy at a genome-wide scale (George et al. 2020) allowing us to explore a vast number of genes associated with a range of phenotypic traits in cancer patients.

Appendix A

Table 12. Full results of association tests for selected SNPs and disease phenotypes isolated and combined. Assuming that D is the minor allele and d is the major allele, the allelic model compares the frequencies of each allele in each group (D x d), the genotypic model is an additive two degree of freedom model that compares the frequency of each genotype in each group (DD x Dd x dd), the trend is the Cochran-Armitage test that does not assume Hardy-Weinberg equilibrium, the dominant model compares the two copies of the common allele versus the sum of the other combinations in each group (dd x DD + Dd), and the recessive model compares the two copies of the rare allele frequency versus the sum other combinations in each group (DD x Dd + dd). DF = degrees of freedom.

Dental caries									
Chromosome	SNP	Allele1/2		TEST	Affected	Unaffected	X^{2}	DF	P-value
17	rs1012117	A	G	GENO	41/220/221	81/345/345	1.351	2	0.509
17	rs1012117	A	G	TREND	302/662	507/1035	0.6743	1	0.4115
17	rs1012117	A	G	ALLELIC	302/662	507/1035	0.6532	1	0.419
17	rs1012117	A	G	DOM	261/221	426/345	0.1458	1	0.7025
17	rs1012117	A	G	REC	41/441	81/690	1.349	1	0.2454
1	rs1010447	T	C	GENO	68/242/253	110/378/363	0.7575	2	0.6847
1	rs1010447	T	C	TREND	378/748	598/1104	0.713	1	0.3985
1	rs1010447	T	C	ALLELIC	378/748	598/1104	0.7343	1	0.3915
1	rs1010447	T	C	DOM	310/253	488/363	0.7178	1	0.3969
1	rs1010447	T	C	REC	68/495	110/741	0.2213	1	0.638
9	rs1050700	C	T	GENO	49/213/201	77/325/323	0.1699	2	0.9186
9	rs1050700	C	T	TREND	311/615	479/971	0.07885	1	0.7789
9	rs1050700	C	T	ALLELIC	311/615	479/971	0.07726	1	0.7811
9	rs1050700	C	T	DOM	262/201	402/323	0.1487	1	0.6997
9	rs1050700	C	T	REC	49/414	77/648	0.0004199	1	0.9837
16	rs1051771	C	G	GENO	3/72/441	6/98/682	0.737	2	0.6917
16	rs1051771	C	G	TREND	78/954	110/1462	0.2851	1	0.5933
16	rs1051771	C	G	ALLELIC	78/954	110/1462	0.2924	1	0.5887
16	rs1051771	C	G	DOM	75/441	104/682	0.494	1	0.5041
16	rs1051771	C	G	REC	3/513	6/780	0.150	1	0.6983
7	rs1109089	T	C	GENO	106/232/183	172/378/254	1.786	2	0.4095
7	rs1109089	T	C	TREND	444/598	722/886	1.263	1	0.2611
7	rs1109089	T	C	ALLELIC	444/598	722/886	1.346	1	0.246
7	rs1109089	T	C	DOM	338/183	550/254	1.785	1	0.1815
7	rs1109089	T	C	REC	106/415	172/632	0.2092	1	0.6474
1	rs11121718	C	T	GENO	3/27/490	5/51/763	0.629	2	0.7299
1	rs11121718	C	T	TREND	33/1007	61/1577	0.5001	1	0.4794
1	rs11121718	C	T	ALLELIC	33/1007	61/1577	0.5702	1	0.4502
1	rs11121718	C	T	DOM	30/490	56/763	0.604	1	0.4370
1	rs11121718	C	T	REC	3/517	5/814	0.006	1	0.9380
1	rs11580061	G	A	GENO	0/34/451	3/64/686	2.873	2	0.2377
1	rs11580061	G	A	TREND	34/936	70/1436	1.884	1	0.1698

1	rs11580061	G	A	ALLELIC	34/936	70/1436	1.915	1	0.1664
1	rs11580061	G	A	DOM	34/451	67/686	1.403	1	0.2319
1	rs11580061	G	A	REC	0/485	3/750	3.112	1	0.0777
17	rs11655020	A	G	GENO	40/256/240	73/441/303	8.037	2	0.01798
17	rs11655020	A	G	TREND	336/736	587/1047	7.078	1	0.007806
17	rs11655020	A	G	ALLELIC	336/736	587/1047	6.044	1	0.01396
17	rs11655020	A	G	DOM	296/240	514/303	7.965	1	0.00477
17	rs11655020	A	G	REC	40/496	73/744	0.9168	1	0.3383
17	rs11651724	A	G	GENO	21/112/170	18/160/353	11.24	2	0.003619
17	rs11651724	A	G	TREND	154/452	196/866	11.08	1	0.0008728
17	rs11651724	A	G	ALLELIC	154/452	196/866	11.26	1	0.000791
17	rs11651724	A	G	DOM	133/170	178/353	8.876	1	0.002889
17	rs11651724	A	G	REC	21/282	18/513	5.426	1	0.01984
5	rs1239265	A	T	GENO	4/16/287	2/22/329	1.278	2	0.5278
5	rs1239265	A	T	TREND	24/590	26/680	0.03806	1	0.8453
5	rs1239265	A	T	ALLELIC	24/590	26/680	0.04606	1	0.8301
5	rs1239265	A	T	DOM	20/287	24/329	0.021	1	0.8839
5	rs1239265	A	T	REC	4/303	2/351	0.988	1	0.3201
5	rs13166875	G	A	GENO	54/175/168	93/264/270	0.5092	2	0.7752
5	rs13166875	G	A	TREND	283/511	450/804	0.01169	1	0.9139
5	rs13166875	G	A	ALLELIC	283/511	450/804	0.01248	1	0.9111
5	rs13166875	G	A	DOM	229/168	357/270	0.05509	1	0.8144
5	rs13166875	G	A	REC	54/343	93/534	0.2994	1	0.5843
5	rs1423688	G	T	GENO	63/197/183	109/280/290	1.37	2	0.504
5	rs1423688	G	T	TREND	323/563	498/860	0.009911	1	0.9207
5	rs1423688	G	T	ALLELIC	323/563	498/860	0.01074	1	0.9175
5	rs1423688	G	T	DOM	260/183	389/290	0.2157	1	0.6424
5	rs1423688	G	T	REC	63/380	109/570	0.6931	1	0.4051
17	rs16947425	A	C	GENO	18/130/353	16/219/546	3.248	2	0.1971
17	rs16947425	A	C	TREND	166/836	251/1311	0.111	1	0.739
17	rs16947425	A	C	ALLELIC	166/836	251/1311	0.111	1	0.739
17	rs16947425	A	C	DOM	148/353	235/546	0.04386	1	0.8341
17	rs16947425	A	C	REC	18/483	16/765	2.819	1	0.09316
17	rs1874087	T	C	GENO	139/208/177	220/337/259	0.6319	2	0.7291
17	rs1874087	T	C	TREND	486/562	777/855	0.3306	1	0.5653
17	rs1874087	T	C	ALLELIC	486/562	777/855	0.3914	1	0.5315
17	rs1874087	T	C	DOM	347/177	557/259	0.604	1	0.437
17	rs1874087	T	C	REC	139/385	220/596	0.03065	1	0.861
17	rs196950	T	C	GENO	99/182/242	146/282/381	0.1808	2	0.9136
17	rs196950	T	C	TREND	380/666	574/1044	0.1619	1	0.6874
17	rs196950	T	C	ALLELIC	380/666	574/1044	0.2011	1	0.6538
17	rs196950	T	C	DOM	281/242	428/381	0.08656	1	0.7686
17	rs196950	T	C	REC	99/424	146/663	0.1647	1	0.6848
17	rs196929	T	C	GENO	64/178/231	99/299/347	0.7866	2	0.6748
17	rs196929	T	C	TREND	306/640	497/993	0.2393	1	0.6247
17	rs196929	T	C	ALLELIC	306/640	497/993	0.2666	1	0.6056
17	rs196929	T	C	DOM	242/231	398/347	0.5926	1	0.4414
17	rs196929	T	C	REC	64/409	99/646	0.01462	1	0.9037
5	rs2043112	A	G	GENO	75/230/201	131/314/315	2.521	2	0.2835
5	rs2043112	A	G	TREND	380/632	576/944	0.02839	1	0.8662
5	rs2043112	A	G	ALLELIC	380/632	576/944	0.03083	1	0.8606
5	rs2043112	A	G	DOM	305/201	445/315	0.3739	1	0.5409
5	rs2043112	A	G	REC	75/431	131/629	1.3	1	0.2542
16	rs2073636	A	G	GENO	60/243/205	101/336/342	2.75	2	0.2529
16	rs2073636	A	G	TREND	363/653	538/1020	0.3829	1	0.5361
16	rs2073636	A	G	ALLELIC	363/653	538/1020	0.3872	1	0.5338
16	rs2073636	A	G	DOM	303/205	437/342	1.584	1	0.2082
16	rs2073636	A	G	REC	60/448	101/678	0.3743	1	0.5406
22	rs2097461	C	T	GENO	79/231/226	120/340/350	0.1794	2	0.9142
22	rs2097461	C	T	TREND	389/683	580/1040	0.06099	1	0.8049
22	rs2097461	C	T	ALLELIC	389/683	580/1040	0.06582	1	0.7975
22	rs2097461	C	T	DOM	310/226	460/350	0.1441	1	0.7043
22	rs2097461	C	T	REC	79/457	120/690	0.001479	1	0.9693

22	rs2239815	C	T	GENO	86/224/220	150/332/329	1.144	2	0.5645
22	rs2239815	C	T	TREND	396/664	632/990	0.6227	1	0.4301
22	rs2239815	C	T	ALLELIC	396/664	632/990	0.6993	1	0.403
22	rs2239815	C	T	DOM	310/220	482/329	0.1177	1	0.7316
22	rs2239815	C	T	REC	86/444	150/661	1.138	1	0.286
17	rs2289764	C	T	GENO	51/182/271	100/272/370	3.707	2	0.1567
17	rs2289764	C	T	TREND	284/724	472/1012	3.291	1	0.06964
17	rs2289764	C	T	ALLELIC	284/724	472/1012	3.745	1	0.05295
17	rs2289764	C	T	DOM	233/271	372/370	1.832	1	0.1759
17	rs2289764	C	T	REC	51/453	100/642	3.178	1	0.07464
7	rs2299967	T	C	GENO	125/263/137	186/399/239	1.37	2	0.5042
7	rs2299967	T	C	TREND	513/537	771/877	1.088	1	0.297
7	rs2299967	T	C	ALLELIC	513/537	771/877	1.105	1	0.2931
7	rs2299967	T	C	DOM	388/137	585/239	1.35	1	0.2452
7	rs2299967	T	C	REC	125/400	186/638	0.2765	1	0.599
7	rs2374261	T	C	GENO	105/211/192	162/344/245	3.705	2	0.1568
7	rs2374261	T	C	TREND	421/595	668/834	2.067	1	0.1505
7	rs2374261	T	C	ALLELIC	421/595	668/834	2.277	1	0.1313
7	rs2374261	T	C	DOM	316/192	506/245	3.577	1	0.05859
7	rs2374261	T	C	REC	105/403	162/589	0.1475	1	0.7009
7	rs3753151	C	T	GENO	86/185/145	115/292/213	0.9701	2	0.6157
7	rs3753151	C	T	TREND	357/475	522/718	0.1271	1	0.7215
7	rs3753151	C	T	ALLELIC	357/475	522/718	0.1344	1	0.7139
7	rs3753151	C	T	DOM	271/145	407/213	0.02762	1	0.868
7	rs3753151	C	T	REC	86/330	115/505	0.7187	1	0.3966
17	rs4255830	G	A	GENO	134/243/139	204/384/220	0.08635	2	0.9577
17	rs4255830	G	A	TREND	511/521	792/824	0.06119	1	0.8046
17	rs4255830	G	A	ALLELIC	511/521	792/824	0.06442	1	0.7996
17	rs4255830	G	A	DOM	377/139	588/220	0.01338	1	0.9079
17	rs4255830	G	A	REC	134/382	204/604	0.08622	1	0.769
17	rs4396582	G	A	GENO	134/252/141	192/372/238	1.377	2	0.5023
17	rs4396582	G	A	TREND	520/534	756/848	1.168	1	0.2798
17	rs4396582	G	A	ALLELIC	520/534	756/848	1.237	1	0.266
17	rs4396582	G	A	DOM	386/141	564/238	1.331	1	0.2487
17	rs4396582	G	A	REC	134/393	192/610	0.3797	1	0.5377
16	rs7187438	C	T	GENO	96/256/178	144/399/267	0.1175	2	0.9429
16	rs7187438	C	T	TREND	448/612	687/933	0.005392	1	0.9415
16	rs7187438	C	T	ALLELIC	448/612	687/933	0.005386	1	0.9415
16	rs7187438	C	T	DOM	352/178	543/267	0.05587	1	0.8131
16	rs7187438	C	T	REC	96/434	144/666	0.02452	1	0.8756

Periodontal disease

Chromosome	SNP	Allele1/2		TEST	Affected	Unaffected	X^{2}	DF	P-value
5	rs2043112	A	G	GENO	6/8/7	45/103/91	1.162	2	0.5592
5	rs2043112	A	G	TREND	20/22	193/285	0.7495	1	0.3866
5	rs2043112	A	G	ALLELIC	20/22	193/285	0.8374	1	0.3601
5	rs2043112	A	G	DOM	14/7	148/91	0.1848	1	0.6673
5	rs2043112	A	G	REC	6/15	45/194	1.162	1	0.281
5	rs1239265	A	T	GENO	0/5/43	12/35/213	2.791	2	0.2477
5	rs1239265	A	T	TREND	5/91	59/461	2.518	1	0.1126
5	rs1239265	A	T	ALLELIC	5/91	59/461	3.279	1	0.07016
5	rs1239265	A	T	DOM	5/43	47/213	1.694	1	0.1930
5	rs1239265	A	T	REC	0/48	12/248	2.305	1	0.1289
5	rs13166875	G	A	GENO	6/8/10	19/58/73	2.558	2	0.2783
5	rs13166875	G	A	TREND	20/28	96/204	1.518	1	0.218
5	rs13166875	G	A	ALLELIC	20/28	96/204	1.74	1	0.1871
5	rs13166875	G	A	DOM	14/10	77/73	0.4064	1	0.5238
5	rs13166875	G	A	REC	6/18	19/131	2.558	1	0.1097
5	rs1423688	G	T	GENO	4/10/17	30/92/102	1.039	2	0.5949
5	rs1423688	G	T	TREND	18/44	152/296	0.5341	1	0.4649
5	rs1423688	G	T	ALLELIC	18/44	152/296	0.5876	1	0.4434
5	rs1423688	G	T	DOM	14/17	122/102	0.947	1	0.3305
5	rs1423688	G	T	REC	4/27	30/194	0.006	1	0.9400

7	rs1109089	T	C	GENO	7/20/25	52/116/107	1.775	2	0.4116
7	rs1109089	T	C	TREND	34/70	220/330	1.748	1	0.1861
7	rs1109089	T	C	ALLELIC	34/70	220/330	1.966	1	0.1608
7	rs1109089	T	C	DOM	27/25	168/107	1.527	1	0.2166
7	rs1109089	T	C	REC	7/45	52/223	0.8776	1	0.3489
7	rs3753151	C	T	GENO	10/21/13	46/120/75	0.3129	2	0.8552
7	rs3753151	C	T	TREND	41/47	212/270	0.2054	1	0.6504
7	rs3753151	C	T	ALLELIC	41/47	212/270	0.205	1	0.6507
7	rs3753151	C	T	DOM	31/13	166/75	0.04324	1	0.8353
7	rs3753151	C	T	REC	10/34	46/195	0.3123	1	0.5763
7	rs2299967	T	C	GENO	14/22/15	68/141/69	1.011	2	0.6033
7	rs2299967	T	C	TREND	50/52	277/279	0.0219	1	0.8824
7	rs2299967	T	C	ALLELIC	50/52	277/279	0.02209	1	0.8818
7	rs2299967	T	C	DOM	36/15	209/69	0.4779	1	0.4894
7	rs2299967	T	C	REC	14/37	68/210	0.206	1	0.6499
7	rs2374261	T	C	GENO	8/19/21	50/109/102	0.4025	2	0.8177
7	rs2374261	T	C	TREND	35/61	209/313	0.3838	1	0.5356
7	rs2374261	T	C	ALLELIC	35/61	209/313	0.4349	1	0.5096
7	rs2374261	T	C	DOM	27/21	159/102	0.369	1	0.5436
7	rs2374261	T	C	REC	8/40	50/211	0.1649	1	0.6847
9	rs1050700	C	T	GENO	10/19/14	42/81/118	3.949	2	0.1388
9	rs1050700	C	T	TREND	39/47	165/317	3.172	1	0.07489
9	rs1050700	C	T	ALLELIC	39/47	165/317	3.918	1	0.04776
9	rs1050700	C	T	DOM	29/14	123/118	3.947	1	0.04694
9	rs1050700	C	T	REC	10/33	42/199	0.8287	1	0.3626
16	rs2073636	A	G	GENO	5/16/19	29/101/103	0.1722	2	0.9175
16	rs2073636	A	G	TREND	26/54	159/307	0.07667	1	0.7819
16	rs2073636	A	G	ALLELIC	26/54	159/307	0.08	1	0.7773
16	rs2073636	A	G	DOM	21/19	130/103	0.1499	1	0.6987
16	rs2073636	A	G	REC	5/35	29/204	9.012e-005	1	0.9924
16	rs7187438	C	T	GENO	14/22/14	56/115/84	0.9932	2	0.6086
16	rs7187438	C	T	TREND	50/50	227/283	0.9293	1	0.3351
16	rs7187438	C	T	ALLELIC	50/50	227/283	1.017	1	0.3133
16	rs7187438	C	T	DOM	36/14	171/84	0.468	1	0.4939
16	rs7187438	C	T	REC	14/36	56/199	0.8622	1	0.3531
16	rs1051771	C	G	GENO	0/1/41	3/0/157	4.598	2	0.1003
16	rs1051771	C	G	TREND	1/83	6/314	0.09873	1	0.7534
16	rs1051771	C	G	ALLELIC	1/83	6/314	0.1831	1	0.6687
16	rs1051771	C	G	DOM	1/41	3/157	0.044	1	0.8340
16	rs1051771	C	G	REC	0/42	3/157	0.799	1	0.3712
17	rs196929	T	C	GENO	14/15/12	37/86/93	6.723	2	0.03468
17	rs196929	T	C	TREND	43/39	160/272	5.809	1	0.01594
17	rs196929	T	C	ALLELIC	43/39	160/272	6.842	1	0.008906
17	rs196929	T	C	DOM	29/12	123/93	2.711	1	0.09967
17	rs196929	T	C	REC	14/27	37/179	6.273	1	0.01226
17	rs16947425	A	C	GENO	2/14/40	9/69/197	0.013	2	0.9935
17	rs16947425	A	C	TREND	18/94	87/463	0.004217	1	0.9482
17	rs16947425	A	C	ALLELIC	18/94	87/463	0.004472	1	0.9467
17	rs16947425	A	C	DOM	16/40	78/197	0.001	1	0.9749
17	rs16947425	A	C	REC	2/54	9/266	0.013	1	0.9095
17	rs196950	T	C	GENO	20/17/19	66/84/116	3.115	2	0.2107
17	rs196950	T	C	TREND	57/55	216/316	2.955	1	0.0856
17	rs196950	T	C	ALLELIC	57/55	216/316	4.013	1	0.04516
17	rs196950	T	C	DOM	37/19	150/116	1.78	1	0.1821
17	rs196950	T	C	REC	20/36	66/200	2.809	1	0.09374
17	rs1874087	C	T	GENO	18/18/8	44/57/56	5.345	2	0.06907
17	rs1874087	C	T	TREND	54/34	145/169	5.058	1	0.02452
17	rs1874087	C	T	ALLELIC	54/34	145/169	6.341	1	0.0118
17	rs1874087	C	T	DOM	36/8	101/56	4.843	1	0.02777
17	rs1874087	C	T	REC	18/26	44/113	2.674	1	0.102
17	rs11655020	A	G	GENO	1/11/38	11/29/224	4.915	2	0.0856
17	rs11655020	A	G	TREND	13/87	51/477	0.7862	1	0.3752
17	rs11655020	A	G	ALLELIC	13/87	51/477	1.025	1	0.3113

17	rs11655020	A	G	DOM	12/38	40/224	2.382	1	0.1227
17	rs11655020	A	G	REC	1/49	11/253	0.537	1	0.4637
17	rs4255830	A	G	GENO	10/27/16	76/131/73	1.627	2	0.4434
17	rs4255830	A	G	TREND	47/59	283/277	1.302	1	0.2538
17	rs4255830	A	G	ALLELIC	47/59	283/277	1.369	1	0.242
17	rs4255830	A	G	DOM	37/16	207/73	0.3858	1	0.5345
17	rs4255830	A	G	REC	10/43	76/204	1.593	1	0.2069
17	rs4396582	G	A	GENO	8/18/20	54/118/91	1.344	2	0.5106
17	rs4396582	G	A	TREND	34/58	226/300	1.058	1	0.3038
17	rs4396582	G	A	ALLELIC	34/58	226/300	1.16	1	0.2814
17	rs4396582	G	A	DOM	26/20	172/91	1.34	1	0.2469
17	rs4396582	G	A	REC	8/38	54/209	0.2408	1	0.6236
17	rs11651724	A	G	GENO	0/9/44	12/43/214	2.458	2	0.2926
17	rs11651724	A	G	TREND	9/97	67/471	1.091	1	0.2962
17	rs11651724	A	G	ALLELIC	9/97	67/471	1.336	1	0.2477
17	rs11651724	A	G	DOM	9/44	55/214	0.334	1	0.5634
17	rs11651724	A	G	REC	0/53	12/257	2.456	1	0.1170
17	rs2289764	C	T	GENO	11/17/14	36/80/114	4.594	2	0.1006
17	rs2289764	C	T	TREND	39/45	152/308	4.588	1	0.03219
17	rs2289764	C	T	ALLELIC	39/45	152/308	5.586	1	0.01811
17	rs2289764	C	T	DOM	28/14	116/114	3.756	1	0.05262
17	rs2289764	C	T	REC	11/31	36/194	2.759	1	0.09669
22	rs2097461	C	T	GENO	8/25/20	42/110/125	1.158	2	0.5604
22	rs2097461	C	T	TREND	41/65	194/360	0.4695	1	0.4932
22	rs2097461	C	T	ALLELIC	41/65	194/360	0.5202	1	0.4708
22	rs2097461	C	T	DOM	33/20	152/125	0.9865	1	0.3206
22	rs2097461	C	T	REC	8/45	42/235	0.0001606	1	0.9899
22	rs2239815	C	T	GENO	11/22/12	51/115/104	2.428	2	0.2971
22	rs2239815	C	T	TREND	44/46	217/323	2.182	1	0.1396
22	rs2239815	C	T	ALLELIC	44/46	217/323	2.408	1	0.1207
22	rs2239815	C	T	DOM	33/12	166/104	2.329	1	0.127
22	rs2239815	C	T	REC	11/34	51/219	0.7531	1	0.3855
17	rs1012117	A	G	GENO	8/2/5	35/7/29	0.36	2	0.8352
17	rs1012117	A	G	TREND	18/12	77/65	0.334	1	0.5633
17	rs1012117	A	G	ALLELIC	18/12	77/65	0.334	1	0.5633
17	rs1012117	A	G	DOM	10/5	42/29	0.292	1	0.5887
17	rs1012117	A	G	REC	8/7	35/36	0.081	1	0.7762

Periapical Lesions

Chromosome	SNP	Allele1/2		TEST	Affected	Unaffected	$X^{2.}$	DF	P-value
5	rs1239265	A	T	GENO	10/42/42	2/6/124	68.38	2	5.461e-016
5	rs1239265	A	T	TREND	62/126	10/254	57.88	1	2.779e-014
5	rs1239265	A	T	ALLELIC	62/126	10/254	69.87	1	6.341e-017
5	rs1239265	A	T	DOM	52/42	8/124	68.31	1	4.231e-016
5	rs1239265	A	T	REC	10/84	2/130	9.089	1	0.00284
7	rs3753151	C	T	GENO	2/39/18	33/49/45	17.17	2	0.00019
7	rs3753151	C	T	TREND	43/75	115/139	2.495	1	0.1142
7	rs3753151	C	T	ALLELIC	43/75	115/139	2.574	1	0.1086
7	rs3753151	C	T	DOM	41/18	82/45	0.436	1	0.5069
7	rs3753151	C	T	REC	2/57	33/94	13.463	1	0.00024
7	rs2299967	C	T	GENO	17/38/20	36/63/36	0.4661	2	0.7921
7	rs2299967	C	T	TREND	72/78	135/135	0.1487	1	0.6998
7	rs2299967	C	T	ALLELIC	72/78	135/135	0.1543	1	0.6944
7	rs2299967	C	T	DOM	55/20	99/36	1.164e-031	1	1
7	rs2299967	C	T	REC	17/58	36/99	0.4088	1	0.5226
7	rs1109089	T	C	GENO	16/37/41	31/51/42	2.954	2	0.2283
7	rs1109089	T	C	TREND	69/119	113/135	2.952	1	0.08578
7	rs1109089	T	C	ALLELIC	69/119	113/135	3.454	1	0.06311
7	rs1109089	T	C	DOM	53/41	82/42	2.154	1	0.1422
7	rs1109089	T	C	REC	16/78	31/93	2.013	1	0.156
9	rs1050700	C	T	GENO	6/34/31	11/40/68	3.908	2	0.1417
9	rs1050700	C	T	TREND	46/96	62/176	1.687	1	0.194
9	rs1050700	C	T	ALLELIC	46/96	62/176	1.759	1	0.1847

9	rs1050700	C	T	DOM	40/31	51/68	3.238	1	0.07193
9	rs1050700	C	T	REC	6/65	11/108	0.03432	1	0.853
16	rs7187438	C	T	GENO	12/25/27	17/51/37	1.458	2	0.4823
16	rs7187438	C	T	TREND	49/79	85/125	0.151	1	0.6976
16	rs7187438	C	T	ALLELIC	49/79	85/125	0.1601	1	0.689
16	rs7187438	C	T	DOM	37/27	68/37	0.8162	1	0.3663
16	rs7187438	C	T	REC	12/52	17/88	0.1833	1	0.6686
16	rs2073636	A	G	GENO	11/40/47	17/54/42	2.599	2	0.2727
16	rs2073636	A	G	TREND	62/134	88/138	2.379	1	0.123
16	rs2073636	A	G	ALLELIC	62/134	88/138	2.445	1	0.1179
16	rs2073636	A	G	DOM	51/47	71/42	2.506	1	0.1134
16	rs2073636	A	G	REC	11/87	17/96	0.6653	1	0.4147
16	rs1051771	C	G	GENO	2/14/68	2/19/103	0.024	2	0.9883
16	rs1051771	C	G	TREND	18/150	23/225	0.2112	1	0.6459
16	rs1051771	C	G	ALLELIC	18/150	23/225	0.2338	1	0.6287
16	rs1051771	C	G	DOM	16/68	21/103	0.153	1	0.6959
16	rs1051771	C	G	REC	2/82	2/122	0.157	1	0.6922
17	rs196929	T	C	GENO	11/27/23	15/46/64	3.245	2	0.1974
17	rs196929	T	C	TREND	49/73	76/174	3.127	1	0.07702
17	rs196929	T	C	ALLELIC	49/73	76/174	3.503	1	0.06124
17	rs196929	T	C	DOM	38/23	61/64	2.999	1	0.08333
17	rs196929	T	C	REC	11/50	15/110	1.241	1	0.2653
17	rs196950	T	C	GENO	16/31/29	15/39/58	3.861	2	0.1451
17	rs196950	T	C	TREND	63/89	69/155	3.807	1	0.05104
17	rs196950	T	C	ALLELIC	63/89	69/155	4.503	1	0.03383
17	rs196950	T	C	DOM	47/29	54/58	3.382	1	0.0659
17	rs196950	T	C	REC	16/60	15/97	1.929	1	0.1649
17	rs16947425	A	C	GENO	1/19/43	5/27/93	2.237	2	0.326
17	rs16947425	A	C	TREND	21/105	37/213	0.2106	1	0.6463
17	rs16947425	A	C	ALLELIC	21/105	37/213	0.2238	1	0.6362
17	rs16947425	A	C	DOM	20/43	32/93	0.791	1	0.3738
17	rs16947425	A	C	REC	1/62	5/120	0.789	1	0.3743
17	rs11655020	A	G	GENO	2/13/82	1/13/118	1.499	2	0.4726
17	rs11655020	A	G	TREND	17/177	15/249	1.45	1	0.2285
17	rs11655020	A	G	ALLELIC	17/177	15/249	1.633	1	0.2012
17	rs11655020	A	G	DOM	15/82	14/118	1.193	1	0.2774
17	rs11655020	A	G	REC	2/95	1/131	0.736	1	0.3910
17	rs4255830	A	G	GENO	12/41/24	36/68/32	3.778	2	0.1512
17	rs4255830	A	G	TREND	65/89	140/132	3.466	1	0.06265
17	rs4255830	A	G	ALLELIC	65/89	140/132	3.379	1	0.06602
17	rs4255830	A	G	DOM	53/24	104/32	1.481	1	0.2237
17	rs4255830	A	G	REC	12/65	36/100	3.338	1	0.06771
17	rs11651724	A	G	GENO	4/15/43	2/22/92	3.738	2	0.1542
17	rs11651724	A	G	TREND	23/101	26/206	3.263	1	0.07084
17	rs11651724	A	G	ALLELIC	23/101	26/206	3.669	1	0.05542
17	rs11651724	A	G	DOM	19/43	24/92	2.186	1	0.1393
17	rs11651724	A	G	REC	4/58	2/114	2.772	1	0.0959
17	rs1012117	A	G	GENO	6/33/32	12/42/64	2.195	2	0.3338
17	rs1012117	A	G	TREND	45/97	66/170	0.5681	1	0.451
17	rs1012117	A	G	ALLELIC	45/97	66/170	0.5928	1	0.4413
17	rs1012117	A	G	DOM	39/32	54/64	1.49	1	0.2222
17	rs1012117	A	G	REC	6/65	12/106	0.152	1	0.6967
22	rs2239815	C	T	GENO	8/45/25	20/45/47	5.972	2	0.05049
22	rs2239815	C	T	TREND	61/95	85/139	0.05201	1	0.8196
22	rs2239815	C	T	ALLELIC	61/95	85/139	0.05195	1	0.8197
22	rs2239815	C	T	DOM	53/25	65/47	1.92	1	0.1659
22	rs2239815	C	T	REC	8/70	20/92	2.114	1	0.146
22	rs2097461	C	T	GENO	8/40/27	18/38/52	6.055	2	0.04844
22	rs2097461	C	T	TREND	56/94	74/142	0.3415	1	0.559
22	rs2097461	C	T	ALLELIC	56/94	74/142	0.3653	1	0.5456
22	rs2097461	C	T	DOM	48/27	56/52	2.663	1	0.1027
22	rs2097461	C	T	REC	8/67	18/90	1.307	1	0.2529
17	rs2289764	C	T	GENO	33/13/44	15/34/58	0.617	2	0.7345

17	rs2289764	C	T	TREND	79/93	64/150	10.5	1	0.00119
17	rs2289764	C	T	ALLELIC	79/93	64/150	10.5	1	0.00119
17	rs2289764	C	T	DOM	46/44	49/58	0.553	1	0.4569
17	rs2289764	C	T	REC	33/57	15/92	13.60	1	0.000225
17	rs4396582	G	A	GENO	23/42/32	29/73/39	1.661	2	0.4357
17	rs4396582	G	A	TREND	88/106	131/151	0.055	1	0.8141
17	rs4396582	G	A	ALLELIC	88/106	131/151	0.055	1	0.8141
17	rs4396582	G	A	DOM	65/32	102/39	0.78	1	0.3771
17	rs4396582	G	A	REC	23/74	29/112	0.333	1	0.5640
7	rs2374261	T	C	GENO	11/29/24	26/44/34	1.963	2	0.375
7	rs2374261	T	C	TREND	51/77	96/112	1.282	1	0.2575
7	rs2374261	T	C	ALLELIC	51/77	96/112	2.085	1	0.148
7	rs2374261	T	C	DOM	40/24	70/34	0.405	1	0.5244
7	rs2374261	T	C	REC	11/53	26/78	1.408	1	0.2353

Osteoporosis

Chromosome	SNP	Allele1/2		TEST	Affected	Unaffected	$X^{2.}$	DF	P-value
1	rs1010447	T	C	GENO	1/6/3	74/228/228	1.153	2	0.5618
1	rs1010447	T	C	TREND	8/12	376/684	0.1666	1	0.6832
1	rs1010447	T	C	ALLELIC	8/12	376/684	0.1757	1	0.6751
1	rs1010447	T	C	DOM	7/3	302/228	0.68	1	0.4097
1	rs1010447	T	C	REC	1/9	74/456	0.129	1	0.7196
1	rs11580061	G	A	GENO	3/1/14	0/25/428	55.482	2	0.000047
1	rs11580061	G	A	TREND	7/29	25/881	25.34	1	4.794e-007
1	rs11580061	G	A	ALLELIC	7/29	25/881	29.37	1	5.971e-008
1	rs11580061	G	A	DOM	4/14	25/428	8.36	1	0.00384
1	rs11580061	G	A	REC	3/15	0/453	75.98	1	0.000032
1	rs11121718	C	T	GENO	0/2/15	3/30/465	1.021	2	0.6002
1	rs11121718	C	T	TREND	2/32	36/960	0.4228	1	0.5155
1	rs11121718	C	T	ALLELIC	2/32	36/960	0.4759	1	0.4903
1	rs11121718	C	T	DOM	2/15	33/465	0.685	1	0.4078
1	rs11121718	C	T	REC	0/17	3/495	0.103	1	0.7482
5	rs2043112	A	G	GENO	2/7/8	80/195/215	0.257	2	0.8793
5	rs2043112	A	G	TREND	11/23	355/625	0.1879	1	0.6647
5	rs2043112	A	G	ALLELIC	11/23	355/625	0.2135	1	0.644
5	rs2043112	A	G	DOM	9/8	275/215	0.067	1	0.7950
5	rs2043112	A	G	REC	2/15	80/410	0.252	1	0.6155
5	rs1239265	A	T	GENO	2/0/12	2/10/183	12.811	2	0.001653
5	rs1239265	A	T	TREND	4/24	14/376	5.11	1	0.02379
5	rs1239265	A	T	ALLELIC	4/24	14/376	7.253	1	0.007079
5	rs1239265	A	T	DOM	2/12	12/183	1.382	1	0.23975
5	rs1239265	A	T	REC	2/12	2/193	12.23	1	0.00047
5	rs13166875	G	A	GENO	2/7/7	54/159/193	0.136	2	0.9340
5	rs13166875	G	A	TREND	11/21	267/545	0.02801	1	0.8671
5	rs13166875	G	A	ALLELIC	11/21	267/545	0.03108	1	0.8601
5	rs13166875	G	A	DOM	9/7	213/193	0.089	1	0.7660
5	rs13166875	G	A	REC	2/14	54/352	0.009	1	0.0743
5	rs1423688	G	T	GENO	3/9/3	80/164/179	3.398	2	0.1828
5	rs1423688	G	T	TREND	15/15	324/522	1.432	1	0.2314
5	rs1423688	G	T	ALLELIC	15/15	324/522	1.672	1	0.1959
5	rs1423688	G	T	DOM	12/3	244/179	2.971	1	0.0847
5	rs1423688	G	T	REC	3/12	80/343	0.011	1	0.9158
7	rs1109089	T	C	GENO	0/12/7	98/231/167	4.875	2	0.0873
7	rs1109089	T	C	TREND	12/26	427/565	1.9	1	0.1681
7	rs1109089	T	C	ALLELIC	12/26	427/565	1.967	1	0.1607
7	rs1109089	T	C	DOM	12/7	329/167	0.082	1	0.7741
7	rs1109089	T	C	REC	0/19	98/398	4.636	1	0.0313
7	rs3753151	C	T	GENO	4/10/4	86/182/126	0.844	2	0.6566
7	rs3753151	C	T	TREND	18/18	354/434	0.3382	1	0.5609
7	rs3753151	C	T	ALLELIC	18/18	354/434	0.3582	1	0.5495
7	rs3753151	C	T	DOM	14/4	268/126	0.759	1	0.3836
7	rs3753151	C	T	REC	4/14	86/308	0.002	1	0.9657
7	rs2299967	T	C	GENO	2/12/4	118/249/138	2.354	2	0.3081

7	rs2299967	T	C	TREND	16/20	485/525	0.178	1	0.6731
7	rs2299967	T	C	ALLELIC	16/20	485/525	0.1781	1	0.673
7	rs2299967	T	C	DOM	14/4	367/138	0.229	1	0.6323
7	rs2299967	T	C	REC	2/16	118/387	1.476	1	0.2243
7	rs2374261	T	C	GENO	3/5/6	97/201/169	0.339	2	0.8439
7	rs2374261	T	C	TREND	11/17	395/539	0.08972	1	0.7645
7	rs2374261	T	C	ALLELIC	11/17	395/539	0.1007	1	0.751
7	rs2374261	T	C	DOM	8/6	298/169	0.261	1	0.6093
7	rs2374261	T	C	REC	3/11	97/370	0.004	1	0.9523
9	rs1050700	C	T	GENO	2/7/8	40/214/191	0.367	2	0.8321
9	rs1050700	C	T	TREND	11/23	294/596	0.007473	1	0.9311
9	rs1050700	C	T	ALLELIC	11/23	294/596	0.006864	1	0.934
9	rs1050700	C	T	DOM	9/8	254/191	0.114	1	0.7352
9	rs1050700	C	T	REC	2/15	40/405	0.153	1	0.6959
16	rs2073636	A	G	GENO	4/5/8	63/232/198	2.74	2	0.254
16	rs2073636	A	G	TREND	13/21	358/628	0.05295	1	0.818
16	rs2073636	A	G	ALLELIC	13/21	358/628	0.05273	1	0.8184
16	rs2073636	A	G	DOM	9/8	295/198	0.325	1	0.5688
16	rs2073636	A	G	REC	4/13	63/430	1.593	1	0.2069
16	rs7187438	C	T	GENO	5/8/4	100/237/159	1.065	2	0.5871
16	rs7187438	C	T	TREND	18/16	437/555	1.019	1	0.3127
16	rs7187438	C	T	ALLELIC	18/16	437/555	1.052	1	0.305
16	rs7187438	C	T	DOM	13/4	337/159	0.551	1	0.4577
16	rs7187438	C	T	REC	5/12	100/396	0.864	1	0.3526
16	rs1051771	C	G	GENO	2/2/13	3/60/416	20.417	2	4.0e-5
16	rs1051771	C	G	TREND	6/28	66/892	5.268	1	0.02172
16	rs1051771	C	G	ALLELIC	6/28	66/892	5.645	1	0.0175
16	rs1051771	C	G	DOM	4/13	63/416	1.513	1	0.2186
16	rs1051771	C	G	REC	2/15	3/476	20.41	1	1.0e-5
17	rs196929	T	C	GENO	4/7/7	63/193/210	1.122	2	0.5705
17	rs196929	T	C	TREND	15/21	319/613	0.7818	1	0.3766
17	rs196929	T	C	ALLELIC	15/21	319/613	0.8488	1	0.3569
17	rs196929	T	C	DOM	11/7	256/210	0.267	1	0.6052
17	rs196929	T	C	REC	4/14	63/403	1.101	1	0.2941
17	rs16947425	A	C	GENO	5/4/10	12/145/320	31.303	2	5.0e-5
17	rs16947425	A	C	TREND	14/24	169/785	8.873	1	0.002895
17	rs16947425	A	C	ALLELIC	14/24	169/785	8.887	1	0.002872
17	rs16947425	A	C	DOM	9/10	157/320	1.714	1	0.1904
17	rs16947425	A	C	REC	5/14	12/465	31.27	1	0.00021
17	rs196950	T	C	GENO	5/6/5	98/171/228	1.8	2	0.4066
17	rs196950	T	C	TREND	16/16	367/627	1.795	1	0.1803
17	rs196950	T	C	ALLELIC	16/16	367/627	2.267	1	0.1322
17	rs196950	T	C	DOM	11/5	269/228	1.337	1	0.2475
17	rs196950	T	C	REC	5/11	98/399	1.285	1	0.2571
17	rs1874087	T	C	GENO	8/7/3	143/207/156	2.746	2	0.2533
17	rs1874087	T	C	TREND	23/13	493/519	2.707	1	0.09992
17	rs1874087	T	C	ALLELIC	23/13	493/519	3.202	1	0.07354
17	rs1874087	T	C	DOM	15/3	350/156	1.65	1	0.199
17	rs1874087	T	C	REC	8/10	143/363	2.219	1	0.1362
17	rs11655020	A	G	GENO	5/7/5	53/253/199	5.98	2	0.05029
17	rs11655020	A	G	TREND	17/17	359/651	3.244	1	0.07166
17	rs11655020	A	G	ALLELIC	17/17	359/651	2.983	1	0.08416
17	rs11655020	A	G	DOM	12/5	306/199	0.69	1	0.4062
17	rs11655020	A	G	REC	5/12	53/452	5.959	1	0.01464
17	rs4255830	G	A	GENO	4/10/5	118/243/139	0.126	2	0.9389
17	rs4255830	G	A	TREND	18/20	479/521	0.004051	1	0.9493
17	rs4255830	G	A	ALLELIC	18/20	479/521	0.004145	1	0.9487
17	rs4255830	G	A	DOM	14/5	361/139	0.02	1	0.8872
17	rs4255830	G	A	REC	4/15	118/382	0.066	1	0.7971
17	rs4396582	G	A	GENO	5/10/4	118/239/133	0.345	2	0.8413
17	rs4396582	G	A	TREND	20/18	475/505	0.2485	1	0.6181
17	rs4396582	G	A	ALLELIC	20/18	475/505	0.2537	1	0.6145
17	rs4396582	G	A	DOM	15/4	357/133	0.345	1	0.5570

17	rs4396582	G	A	REC	5/14	118/372	0.05	1	0.8233
17	rs11651724	A	G	GENO	3/1/11	12/103/234	12.284	2	0.00215
17	rs11651724	A	G	TREND	7/23	127/571	0.4822	1	0.4874
17	rs11651724	A	G	ALLELIC	7/23	127/571	0.5057	1	0.477
17	rs11651724	A	G	DOM	4/11	115/234	0.258	1	0.6114
17	rs11651724	A	G	REC	3/12	12/337	9.984	1	0.00158
17	rs2289764	C	T	GENO	5/3/8	57/165/239	5.528	2	0.06303
17	rs2289764	C	T	TREND	13/19	279/643	1.336	1	0.2478
17	rs2289764	C	T	ALLELIC	13/19	279/643	1.564	1	0.211
17	rs2289764	C	T	DOM	8/8	222/239	0.021	1	0.8846
17	rs2289764	C	T	REC	5/11	57/404	4.877	1	0.0272
17	rs1012117	A	G	GENO	5/5/5	53/213/215	7.015	2	0.02998
17	rs1012117	A	G	TREND	15/15	319/643	3.636	1	0.05654
17	rs1012117	A	G	ALLELIC	15/15	319/643	3.694	1	0.0546
17	rs1012117	A	G	DOM	10/5	266/215	0.7613	1	0.3829
17	rs1012117	A	G	REC	5/10	53/428	7.014	1	0.008085
22	rs2097461	C	T	GENO	7/5/4	71/211/228	11.06	2	0.00396
22	rs2097461	C	T	TREND	19/13	353/667	7.558	1	0.005975
22	rs2097461	C	T	ALLELIC	19/13	353/667	8.327	1	0.003907
22	rs2097461	C	T	DOM	12/4	282/228	2.444	1	0.118
22	rs2097461	C	T	REC	7/9	71/439	10.93	1	0.00095
22	rs2239815	C	T	GENO	7/6/5	90/203/212	5.209	2	0.07394
22	rs2239815	C	T	TREND	20/16	383/627	3.947	1	0.04695
22	rs2239815	C	T	ALLELIC	20/16	383/627	4.564	1	0.03264
22	rs2239815	C	T	DOM	13/5	293/212	1.444	1	0.2295
22	rs2239815	C	T	REC	7/11	90/415	5.106	1	0.02384
Temporomandibular joint symptoms									
Chromosome	SNP	Allele1/2		TEST	Affected	Unaffected	X^2	DF	P-value
17	rs196929	T	C	GENO	67/174/256	81/231/328	0.242	2	0.886
17	rs196929	T	C	TREND	308/686	393/887	0.01801	1	0.8932
17	rs196929	T	C	ALLELIC	308/686	393/887	0.02098	1	0.8848
17	rs196929	T	C	DOM	241/256	312/328	0.007515	1	0.9309
17	rs196929	T	C	REC	67/430	81/559	0.168	1	0.6819
17	rs196950	T	C	GENO	95/170/218	114/197/309	2.449	2	0.294
17	rs196950	T	C	TREND	360/606	425/815	1.665	1	0.1969
17	rs196950	T	C	ALLELIC	360/606	425/815	2.122	1	0.1452
17	rs196950	T	C	DOM	265/218	311/309	2.408	1	0.1207
17	rs196950	T	C	REC	95/388	114/506	0.2904	1	0.59
17	rs1874087	T	C	GENO	106/177/180	142/253/222	1.11	2	0.5742
17	rs1874087	T	C	TREND	389/537	537/697	0.414	1	0.52
17	rs1874087	T	C	ALLELIC	389/537	537/697	0.4914	1	0.4833
17	rs1874087	T	C	DOM	283/180	395/222	0.9496	1	0.3298
17	rs1874087	T	C	REC	106/357	142/475	0.002168	1	0.9629
17	rs1665020	A	G	GENO	40/105/294	53/167/328	5.842	2	0.05388
17	rs1665020	A	G	TREND	185/693	273/823	3.285	1	0.0699
17	rs1665020	A	G	ALLELIC	185/693	273/823	4.03	1	0.04469
17	rs1665020	A	G	DOM	145/294	220/328	5.297	1	0.02137
17	rs1665020	A	G	REC	40/399	53/495	0.08953	1	0.7648
22	rs2097461	C	T	GENO	69/213/182	81/266/273	2.629	2	0.2687
22	rs2097461	C	T	TREND	351/577	428/812	2.424	1	0.1195
22	rs2097461	C	T	ALLELIC	351/577	428/812	2.522	1	0.1123
22	rs2097461	C	T	DOM	282/182	347/273	2.519	1	0.1125
22	rs2097461	C	T	REC	69/395	81/539	0.7261	1	0.3941
22	rs2239815	C	T	GENO	72/197/183	92/244/265	1.402	2	0.4962
22	rs2239815	C	T	TREND	341/563	428/774	0.9069	1	0.3409
22	rs2239815	C	T	ALLELIC	341/563	428/774	0.9946	1	0.3186
22	rs2239815	C	T	DOM	269/183	336/265	1.373	1	0.2414
22	rs2239815	C	T	REC	72/380	92/509	0.07576	1	0.7831
Dental caries and periodontal disease combined									
Chromosome	SNP	Allele1/2		TEST	Affected	Unaffected	X^2	DF	P-value
12	rs1012117	A	G	GENO	17/115/120	47/176/187	3.989	2	0.1361
12	rs1012117	A	G	TREND	149/355	270/550	1.659	1	0.1977

12	rs1012117	A	G	ALLELIC	149/355	270/550	1.632	1	0.2014
12	rs1012117	A	G	DOM	132/120	223/187	0.2534	1	0.6147
12	rs1012117	A	G	REC	17/235	47/363	3.977	1	0.04612
12	rs1010447	T	C	GENO	41/137/137	57/204/186	0.3544	2	0.8376
12	rs1010447	T	C	TREND	219/411	318/576	0.1039	1	0.7473
12	rs1010447	T	C	ALLELIC	219/411	318/576	0.1059	1	0.7449
12	rs1010447	T	C	DOM	178/137	261/186	0.2678	1	0.6048
12	rs1010447	T	C	REC	41/274	57/390	0.01151	1	0.9146
12	rs1050700	C	T	GENO	27/109/117	35/169/174	0.4003	2	0.8186
12	rs1050700	C	T	TREND	163/343	239/517	0.05097	1	0.8214
12	rs1050700	C	T	ALLELIC	163/343	239/517	0.05022	1	0.8227
12	rs1050700	C	T	DOM	136/117	204/174	0.002775	1	0.958
12	rs1050700	C	T	REC	27/226	35/343	0.3414	1	0.559
12	rs1051771	C	G	GENO	0/36/247	2/51/359	1.39	2	0.4991
12	rs1051771	C	G	TREND	36/530	55/769	0.05546	1	0.8138
12	rs1051771	C	G	ALLELIC	36/530	55/769	0.05419	1	0.8159
12	rs1051771	C	G	DOM	36/247	53/359	0.003	1	0.9557
12	rs1051771	C	G	REC	0/283	2/410	1.378	1	0.2404
12	rs1109089	T	C	GENO	58/119/114	99/192/129	5.545	2	0.06249
12	rs1109089	T	C	TREND	235/347	390/450	4.594	1	0.03209
12	rs1109089	T	C	ALLELIC	235/347	390/450	5.109	1	0.0238
12	rs1109089	T	C	DOM	177/114	291/129	5.47	1	0.01934
12	rs1109089	T	C	REC	58/233	99/321	1.324	1	0.2499
12	rs11655020	A	G	GENO	24/142/130	40/228/159	3.271	2	0.1949
12	rs11655020	A	G	TREND	190/402	308/546	2.817	1	0.09326
12	rs11655020	A	G	ALLELIC	190/402	308/546	2.442	1	0.1181
12	rs11655020	A	G	DOM	166/130	268/159	3.253	1	0.07128
12	rs11655020	A	G	REC	24/272	40/387	0.3437	1	0.5577
12	rs11651724	A	G	GENO	10/53/86	13/95/158	0.6199	2	0.7335
12	rs11651724	A	G	TREND	73/225	121/411	0.326	1	0.568
12	rs11651724	A	G	ALLELIC	73/225	121/411	0.3275	1	0.5672
12	rs11651724	A	G	DOM	63/86	108/158	0.1113	1	0.7387
12	rs11651724	A	G	REC	10/139	13/253	0.6071	1	0.4359
12	rs1239265	A	T	GENO	3/13/160	2/15/185	0.368	2	0.8320
12	rs1239265	A	T	TREND	19/333	19/385	0.1554	1	0.6935
12	rs1239265	A	T	ALLELIC	19/333	19/385	0.1902	1	0.6628
12	rs1239265	A	T	DOM	16/160	17/185	0.054	1	0.8165
12	rs1239265	A	T	REC	3/173	2/200	0.368	1	0.5442
12	rs13166875	G	A	GENO	33/99/85	43/139/142	1.237	2	0.5388
12	rs13166875	G	A	TREND	165/269	225/423	1.171	1	0.2791
12	rs13166875	G	A	ALLELIC	165/269	225/423	1.225	1	0.2684
12	rs13166875	G	A	DOM	132/85	182/142	1.157	1	0.2821
12	rs13166875	G	A	REC	33/184	43/281	0.4033	1	0.5254
12	rs1423688	G	T	GENO	30/114/100	67/151/140	4.52	2	0.1043
12	rs1423688	G	T	TREND	174/314	285/431	1.985	1	0.1589
12	rs1423688	G	T	ALLELIC	174/314	285/431	2.117	1	0.1456
12	rs1423688	G	T	DOM	144/100	218/140	0.2133	1	0.6442
12	rs1423688	G	T	REC	30/214	67/291	4.425	1	0.03542
12	rs16947425	A	C	GENO	6/84/187	8/107/294	1.515	2	0.469
12	rs16947425	A	C	TREND	96/458	123/695	1.344	1	0.2463
12	rs16947425	A	C	ALLELIC	96/458	123/695	1.293	1	0.2554
12	rs16947425	A	C	DOM	90/187	115/294	1.508	1	0.2195
12	rs16947425	A	C	REC	6/271	8/401	0.03646	1	0.8486
12	rs1874087	T	C	GENO	80/118/88	111/177/131	0.1903	2	0.9092
12	rs1874087	T	C	TREND	278/294	399/439	0.1144	1	0.7351
12	rs1874087	T	C	ALLELIC	278/294	399/439	0.133	1	0.7154
12	rs1874087	T	C	DOM	198/88	288/131	0.0195	1	0.8889
12	rs1874087	T	C	REC	80/206	111/308	0.1886	1	0.6641
12	rs196950	T	C	GENO	63/104/122	76/142/205	3.042	2	0.2185
12	rs196950	T	C	TREND	230/348	294/552	2.984	1	0.08409
12	rs196950	T	C	ALLELIC	230/348	294/552	3.751	1	0.05276
12	rs196950	T	C	DOM	167/122	218/205	2.7	1	0.1004
12	rs196950	T	C	REC	63/226	76/347	1.605	1	0.2052

12	rs196929	T	C	GENO	35/98/122	51/145/186	0.04762	2	0.9765
12	rs196929	T	C	TREND	168/342	247/517	0.04599	1	0.8302
12	rs196929	T	C	ALLELIC	168/342	247/517	0.05204	1	0.8195
12	rs196929	T	C	DOM	133/122	196/186	0.04403	1	0.8338
12	rs196929	T	C	REC	35/220	51/331	0.01839	1	0.8921
12	rs2043112	A	G	GENO	39/126/114	52/171/176	0.7139	2	0.6998
12	rs2043112	A	G	TREND	204/354	275/523	0.6076	1	0.4357
12	rs2043112	A	G	ALLELIC	204/354	275/523	0.6327	1	0.4264
12	rs2043112	A	G	DOM	165/114	223/176	0.7085	1	0.3999
12	rs2043112	A	G	REC	39/240	52/347	0.1264	1	0.7222
12	rs2073636	A	G	GENO	28/127/123	53/166/184	2.156	2	0.3403
12	rs2073636	A	G	TREND	183/373	272/534	0.0994	1	0.7525
12	rs2073636	A	G	ALLELIC	183/373	272/534	0.1027	1	0.7486
12	rs2073636	A	G	DOM	155/123	219/184	0.1327	1	0.7157
12	rs2073636	A	G	REC	28/250	53/350	1.489	1	0.2224
12	rs2097461	C	T	GENO	49/115/129	68/176/184	0.269	2	0.8742
12	rs2097461	C	T	TREND	213/373	312/544	0.001344	1	0.9708
12	rs2097461	C	T	ALLELIC	213/373	312/544	0.001517	1	0.9689
12	rs2097461	C	T	DOM	164/129	244/184	0.07609	1	0.7827
12	rs2097461	C	T	REC	49/244	68/360	0.08936	1	0.765
12	rs2239815	C	T	GENO	53/113/120	76/172/173	0.1286	2	0.9377
12	rs2239815	C	T	TREND	219/353	324/518	0.004677	1	0.9455
12	rs2239815	C	T	ALLELIC	219/353	324/518	0.005369	1	0.9416
12	rs2239815	C	T	DOM	166/120	248/173	0.05256	1	0.8187
12	rs2239815	C	T	REC	53/233	76/345	0.02622	1	0.8714
12	rs2289764	C	T	GENO	31/102/145	52/139/203	0.6562	2	0.7203
12	rs2289764	C	T	TREND	164/392	243/545	0.2414	1	0.6232
12	rs2289764	C	T	ALLELIC	164/392	243/545	0.2777	1	0.5982
12	rs2289764	C	T	DOM	133/145	191/203	0.02636	1	0.871
12	rs2289764	C	T	REC	31/247	52/342	0.6308	1	0.4271
12	rs2299967	T	C	GENO	63/137/80	100/201/128	0.2939	2	0.8633
12	rs2299967	T	C	TREND	263/297	401/457	0.006766	1	0.9344
12	rs2299967	T	C	ALLELIC	263/297	401/457	0.007055	1	0.9331
12	rs2299967	T	C	DOM	200/80	301/128	0.1309	1	0.7175
12	rs2299967	T	C	REC	63/217	100/329	0.06279	1	0.8021
12	rs2374261	T	C	GENO	54/110/117	93/179/122	8.239	2	0.01625
12	rs2374261	T	C	TREND	218/344	365/423	6.723	1	0.009516
12	rs2374261	T	C	ALLELIC	218/344	365/423	7.58	1	0.0059
12	rs2374261	T	C	DOM	164/117	272/122	8.169	1	0.004262
12	rs2374261	T	C	REC	54/227	93/301	1.853	1	0.1734
12	rs3753151	C	T	GENO	47/100/88	63/142/119	0.09141	2	0.9553
12	rs3753151	C	T	TREND	194/276	268/380	0.0006728	1	0.9793
12	rs3753151	C	T	ALLELIC	194/276	268/380	0.0007449	1	0.9782
12	rs3753151	C	T	DOM	147/88	205/119	0.03015	1	0.8622
12	rs3753151	C	T	REC	47/188	63/261	0.0266	1	0.8704
12	rs4255830	A	G	GENO	82/131/74	105/196/114	0.9526	2	0.6211
12	rs4255830	A	G	TREND	295/279	406/424	0.7802	1	0.3771
12	rs4255830	A	G	ALLELIC	295/279	406/424	0.8335	1	0.3613
12	rs4255830	A	G	DOM	213/74	301/114	0.2459	1	0.62
12	rs4255830	A	G	REC	82/205	105/310	0.9285	1	0.3353
12	rs4396582	G	A	GENO	75/142/73	114/169/139	6.697	2	0.03514
12	rs4396582	G	A	TREND	292/288	397/447	1.337	1	0.2475
12	rs4396582	G	A	ALLELIC	292/288	397/447	1.505	1	0.2199
12	rs4396582	G	A	DOM	217/73	283/139	4.958	1	0.02598
12	rs4396582	G	A	REC	75/215	114/308	0.117	1	0.7323
12	rs7187438	C	T	GENO	56/141/96	73/205/147	0.5328	2	0.7661
12	rs7187438	C	T	TREND	253/333	351/499	0.4974	1	0.4806
12	rs7187438	C	T	ALLELIC	253/333	351/499	0.503	1	0.4782
12	rs7187438	C	T	DOM	197/96	278/147	0.2576	1	0.6118
12	rs7187438	C	T	REC	56/237	73/352	0.4411	1	0.5066
Dental caries and periapical lesions combined									
Chromosome	SNP	Allele1/2		TEST	Affected	Unaffected	X^2	DF	P-value

1	rs1010447	T	C	GENO	14/46/56	36/127/129	0.6004	2	0.7407
1	rs1010447	T	C	TREND	74/158	199/385	0.3379	1	0.561
1	rs1010447	T	C	ALLELIC	74/158	199/385	0.354	1	0.5518
1	rs1010447	T	C	DOM	60/56	163/129	0.5625	1	0.4533
1	rs1010447	T	C	REC	14/102	36/256	0.005211	1	0.9425
4	rs2043112	A	G	GENO	16/40/49	42/118/111	1.117	2	0.5721
4	rs2043112	A	G	TREND	72/138	202/340	0.5324	1	0.4656
4	rs2043112	A	G	ALLELIC	72/138	202/340	0.5818	1	0.4456
4	rs2043112	A	G	DOM	56/49	160/111	1.008	1	0.3153
4	rs2043112	A	G	REC	16/89	42/229	0.003923	1	0.9501
5	rs1239265	A	T	GENO	2/7/56	2/10/105	0.637	2	0.7271
5	rs1239265	A	T	TREND	11/119	14/220	0.6321	1	0.4266
5	rs1239265	A	T	ALLELIC	11/119	14/220	0.8027	1	0.3703
5	rs1239265	A	T	DOM	9/56	12/105	0.528	1	0.4676
5	rs1239265	A	T	REC	2/63	2/115	0.364	1	0.5465
5	rs13166875	G	A	GENO	11/26/31	30/97/94	0.7511	2	0.6869
5	rs13166875	G	A	TREND	48/88	157/285	0.002173	1	0.9628
5	rs13166875	G	A	ALLELIC	48/88	157/285	0.002326	1	0.9615
5	rs13166875	G	A	DOM	37/31	127/94	0.1976	1	0.6566
5	rs13166875	G	A	REC	11/57	30/191	0.2891	1	0.5908
5	rs1423688	G	T	GENO	11/34/37	46/86/102	1.7	2	0.4275
5	rs1423688	G	T	TREND	56/108	178/290	0.664	1	0.4152
5	rs1423688	G	T	ALLELIC	56/108	178/290	0.7873	1	0.3749
5	rs1423688	G	T	DOM	45/37	132/102	0.05786	1	0.8099
5	rs1423688	G	T	REC	11/71	46/188	1.601	1	0.2058
7	rs1109089	T	C	GENO	12/46/51	57/146/82	12.54	2	0.001893
7	rs1109089	T	C	TREND	70/148	260/310	11.83	1	0.000584
7	rs1109089	T	C	ALLELIC	70/148	260/310	11.81	1	0.0005878
7	rs1109089	T	C	DOM	58/51	203/82	11.45	1	0.0007166
7	rs1109089	T	C	REC	12/97	57/228	4.412	1	0.03569
7	rs3753151	C	T	GENO	26/39/30	39/116/73	4.863	2	0.08791
7	rs3753151	C	T	TREND	91/99	194/262	1.517	1	0.2181
7	rs3753151	C	T	ALLELIC	91/99	194/262	1.558	1	0.212
7	rs3753151	C	T	DOM	65/30	155/73	0.005939	1	0.9386
7	rs3753151	C	T	REC	26/69	39/189	4.394	1	0.03606
7	rs2299967	T	C	GENO	28/53/25	67/143/79	0.7554	2	0.6854
7	rs2299967	T	C	TREND	109/103	277/301	0.7513	1	0.3861
7	rs2299967	T	C	ALLELIC	109/103	277/301	0.7566	1	0.3844
7	rs2299967	T	C	DOM	81/25	210/79	0.5625	1	0.4533
7	rs2299967	T	C	REC	28/78	67/222	0.4434	1	0.5055
7	rs2374261	T	C	GENO	12/44/49	57/133/78	11.73	2	0.002836
7	rs2374261	T	C	TREND	68/142	247/289	11.3	1	0.0007748
7	rs2374261	T	C	ALLELIC	68/142	247/289	11.61	1	0.0006558
7	rs2374261	T	C	DOM	56/49	190/78	10.36	1	0.001286
7	rs2374261	T	C	REC	12/93	57/211	4.845	1	0.02772
9	rs1050700	C	T	GENO	2/41/49	27/115/119	6.372	2	0.04133
9	rs1050700	C	T	TREND	45/139	169/353	4.234	1	0.03963
9	rs1050700	C	T	ALLELIC	45/139	169/353	4.039	1	0.04447
9	rs1050700	C	T	DOM	43/49	142/119	1.603	1	0.2054
9	rs1050700	C	T	REC	2/90	27/234	6.023	1	0.0141
16	rs2073636	A	G	GENO	12/54/43	37/107/128	3.328	2	0.1894
16	rs2073636	A	G	TREND	78/140	181/363	0.4122	1	0.5209
16	rs2073636	A	G	ALLELIC	78/140	181/363	0.4362	1	0.5089
16	rs2073636	A	G	DOM	66/43	144/128	1.821	1	0.1772
16	rs2073636	A	G	REC	12/97	37/235	0.4671	1	0.4943
16	rs7187438	C	T	GENO	25/50/34	48/139/100	2.073	2	0.3547
16	rs7187438	C	T	TREND	100/118	235/339	1.54	1	0.2147
16	rs7187438	C	T	ALLELIC	100/118	235/339	1.574	1	0.2096
16	rs7187438	C	T	DOM	75/34	187/100	0.4702	1	0.4929
16	rs7187438	C	T	REC	25/84	48/239	2.027	1	0.1545
16	rs1051771	C	G	GENO	0/11/95	2/37/239	1.408	2	0.4946
16	rs1051771	C	G	TREND	11/201	41/515	1.15	1	0.2836
16	rs1051771	C	G	ALLELIC	11/201	41/515	1.161	1	0.2812

16	rs1051771	C	G	DOM	11/95	39/239	0.903	1	0.3418
16	rs1051771	C	G	REC	0/106	2/276	1.319	1	0.2508
17	rs196929	T	C	GENO	16/38/48	25/97/138	2.9	2	0.2345
17	rs196929	T	C	TREND	70/134	147/373	2.294	1	0.1298
17	rs196929	T	C	ALLELIC	70/134	147/373	2.55	1	0.1103
17	rs196929	T	C	DOM	54/48	122/138	1.062	1	0.3027
17	rs196929	T	C	REC	16/86	25/235	2.688	1	0.1011
17	rs16947425	A	C	GENO	6/28/71	5/75/193	4.05	2	0.132
17	rs16947425	A	C	TREND	40/170	85/461	1.314	1	0.2517
17	rs16947425	A	C	ALLELIC	40/170	85/461	1.331	1	0.2487
17	rs16947425	A	C	DOM	34/71	80/193	0.3409	1	0.5593
17	rs16947425	A	C	REC	6/99	5/268	4.046	1	0.04427
17	rs196950	T	C	GENO	22/42/46	39/96/143	3.58	2	0.1669
17	rs196950	T	C	TREND	86/134	174/382	3.578	1	0.05855
17	rs196950	T	C	ALLELIC	86/134	174/382	4.3	1	0.03811
17	rs196950	T	C	DOM	64/46	135/143	2.92	1	0.08749
17	rs196950	T	C	REC	22/88	39/239	2.121	1	0.1453
17	rs1874087	T	C	GENO	33/42/36	60/122/91	2.845	2	0.2412
17	rs1874087	T	C	TREND	108/114	242/304	1.046	1	0.3065
17	rs1874087	T	C	ALLELIC	108/114	242/304	1.191	1	0.2751
17	rs1874087	T	C	DOM	75/36	182/91	0.02894	1	0.8649
17	rs1874087	T	C	REC	33/78	60/213	2.584	1	0.108
17	rs11655020	A	G	GENO	9/73/29	28/177/83	0.6694	2	0.7156
17	rs11655020	A	G	TREND	91/131	233/343	0.0276	1	0.8681
17	rs11655020	A	G	ALLELIC	91/131	233/343	0.01935	1	0.8894
17	rs11655020	A	G	DOM	82/29	205/83	0.2878	1	0.5916
17	rs11655020	A	G	REC	9/102	28/260	0.2481	1	0.6184
17	rs4255830	G	A	GENO	21/53/31	64/143/80	0.2678	2	0.8747
17	rs4255830	G	A	TREND	95/115	271/303	0.2419	1	0.6228
17	rs4255830	G	A	ALLELIC	95/115	271/303	0.2408	1	0.6236
17	rs4255830	G	A	DOM	74/31	207/80	0.103	1	0.7482
17	rs4255830	G	A	REC	21/84	64/223	0.2394	1	0.6246
17	rs4396582	A	G	GENO	26/51/32	75/133/70	0.8298	2	0.6604
17	rs4396582	A	G	TREND	103/115	283/273	0.7962	1	0.3722
17	rs4396582	A	G	ALLELIC	103/115	283/273	0.8352	1	0.3608
17	rs4396582	A	G	DOM	77/32	208/70	0.7041	1	0.4014
17	rs4396582	A	G	REC	26/83	75/203	0.3965	1	0.5289
17	rs11651724	A	G	GENO	1/14/37	11/60/111	2.467	2	0.2912
17	rs11651724	A	G	TREND	16/88	82/282	2.386	1	0.1224
17	rs11651724	A	G	ALLELIC	16/88	82/282	2.493	1	0.1144
17	rs11651724	A	G	DOM	15/37	71/111	1.798	1	0.1799
17	rs11651724	A	G	REC	1/51	11/171	1.412	1	0.2347
17	rs2289764	C	T	GENO	15/29/60	24/97/140	3.98	2	0.1367
17	rs2289764	C	T	TREND	59/149	145/377	0.02232	1	0.8812
17	rs2289764	C	T	ALLELIC	59/149	145/377	0.0255	1	0.8731
17	rs2289764	C	T	DOM	44/60	121/140	0.493	1	0.4826
17	rs2289764	C	T	REC	15/89	24/237	2.13	1	0.1445
17	rs1012117	A	G	GENO	10/44/45	25/128/122	0.1686	2	0.9191
17	rs1012117	A	G	TREND	64/134	178/372	0.0001144	1	0.9915
17	rs1012117	A	G	ALLELIC	64/134	178/372	0.0001086	1	0.9917
17	rs1012117	A	G	DOM	54/45	153/122	0.03505	1	0.8515
17	rs1012117	A	G	REC	10/89	25/250	0.08756	1	0.7673
22	rs2097461	C	T	GENO	16/53/42	44/114/138	3.097	2	0.2126
22	rs2097461	C	T	TREND	85/137	202/390	1.115	1	0.291
22	rs2097461	C	T	ALLELIC	85/137	202/390	1.228	1	0.2678
22	rs2097461	C	T	DOM	69/42	158/138	2.525	1	0.112
22	rs2097461	C	T	REC	16/95	44/252	0.01303	1	0.9091
22	rs2239815	C	T	GENO	22/52/37	46/109/126	4.337	2	0.1144
22	rs2239815	C	T	TREND	96/126	201/361	3.355	1	0.06701
22	rs2239815	C	T	ALLELIC	96/126	201/361	3.782	1	0.05181
22	rs2239815	C	T	DOM	74/37	155/126	4.337	1	0.03729
22	rs2239815	C	T	REC	22/89	46/235	0.6604	1	0.4164

Dental caries, periodontal disease and periapical lesions combined									
Chromosome	SNP	Allele1/2		TEST	Affected	Unaffected	X^2	DF	P-value
1	rs1010447	T	C	GENO	11/28/37	23/77/83	0.6399	2	0.7262
1	rs1010447	T	C	TREND	50/102	123/243	0.02247	1	0.8808
1	rs1010447	T	C	ALLELIC	50/102	123/243	0.02446	1	0.8757
1	rs1010447	T	C	DOM	39/37	100/83	0.2393	1	0.6247
1	rs1010447	T	C	REC	11/65	23/160	0.1709	1	0.6793
4	rs2043112	A	G	GENO	7/25/37	23/69/74	1.717	2	0.4239
4	rs2043112	A	G	TREND	39/99	115/217	1.648	1	0.1992
4	rs2043112	A	G	ALLELIC	39/99	115/217	1.8	1	0.1797
4	rs2043112	A	G	DOM	32/37	92/74	1.6	1	0.2059
4	rs2043112	A	G	REC	7/62	23/143	0.6026	1	0.4376
5	rs1239265	A	T	GENO	2/5/37	2/10/83	0.697	2	0.7120
5	rs1239265	A	T	TREND	9/79	14/176	0.5025	1	0.4784
5	rs1239265	A	T	ALLELIC	9/79	14/176	0.6477	1	0.4209
5	rs1239265	A	T	DOM	7/37	12/83	0.274	1	0.3951
5	rs1239265	A	T	REC	2/42	2/93	0.641	1	0.4397
5	rs13166875	G	A	GENO	5/16/21	19/57/59	0.5244	2	0.7693
5	rs13166875	G	A	TREND	26/58	95/175	0.471	1	0.4925
5	rs13166875	G	A	ALLELIC	26/58	95/175	0.5102	1	0.475
5	rs13166875	G	A	DOM	21/21	76/59	0.5127	1	0.474
5	rs13166875	G	A	REC	5/37	19/116	0.1286	1	0.7199
5	rs1423688	G	T	GENO	10/21/22	33/58/57	0.3055	2	0.8583
5	rs1423688	G	T	TREND	41/65	124/172	0.2802	1	0.5965
5	rs1423688	G	T	ALLELIC	41/65	124/172	0.3329	1	0.564
5	rs1423688	G	T	DOM	31/22	91/57	0.1468	1	0.7016
5	rs1423688	G	T	REC	10/43	33/115	0.2729	1	0.6014
7	rs1109089	T	C	GENO	10/25/35	38/89/50	10.53	2	0.005156
7	rs1109089	T	C	TREND	45/95	165/189	8.138	1	0.004334
7	rs1109089	T	C	ALLELIC	45/95	165/189	8.592	1	0.003376
7	rs1109089	T	C	DOM	35/35	127/50	10.51	1	0.001184
7	rs1109089	T	C	REC	10/60	38/139	1.653	1	0.1985
7	rs3753151	C	T	GENO	17/24/21	24/71/47	3.565	2	0.1683
7	rs3753151	C	T	TREND	58/66	119/165	0.7931	1	0.3732
7	rs3753151	C	T	ALLELIC	58/66	119/165	0.8344	1	0.361
7	rs3753151	C	T	DOM	41/21	95/47	0.01159	1	0.9143
7	rs3753151	C	T	REC	17/45	24/118	2.973	1	0.08466
7	rs2299967	T	C	GENO	20/31/17	46/82/53	0.6212	2	0.733
7	rs2299967	T	C	TREND	71/65	174/188	0.6206	1	0.4308
7	rs2299967	T	C	ALLELIC	71/65	174/188	0.6778	1	0.4103
7	rs2299967	T	C	DOM	51/17	128/53	0.4484	1	0.5031
7	rs2299967	T	C	REC	20/48	46/135	0.4055	1	0.5243
7	rs2374261	T	C	GENO	8/25/36	38/83/45	14.07	2	0.0008793
7	rs2374261	T	C	TREND	41/97	159/173	12.44	1	0.0004212
7	rs2374261	T	C	ALLELIC	41/97	159/173	13.18	1	0.0002827
7	rs2374261	T	C	DOM	33/36	121/45	13.56	1	0.0002314
7	rs2374261	T	C	REC	8/61	38/128	3.951	1	0.04683
9	rs1050700	C	T	GENO	1/26/27	11/75/78	1.841	2	0.3982
9	rs1050700	C	T	TREND	28/80	97/231	0.6094	1	0.435
9	rs1050700	C	T	ALLELIC	28/80	97/231	0.5285	1	0.4672
9	rs1050700	C	T	DOM	27/27	86/78	0.097	1	0.7557
9	rs1050700	C	T	REC	1/53	11/153	1.841	1	0.1748
16	rs2073636	A	G	GENO	7/33/31	22/61/85	2.237	2	0.3267
16	rs2073636	A	G	TREND	47/95	105/231	0.1439	1	0.7045
16	rs2073636	A	G	ALLELIC	47/95	105/231	0.1573	1	0.6917
16	rs2073636	A	G	DOM	40/31	83/85	0.9605	1	0.3271
16	rs2073636	A	G	REC	7/64	22/146	0.4902	1	0.4838
16	rs7187438	C	T	GENO	17/33/19	31/78/70	3.437	2	0.1793
16	rs7187438	C	T	TREND	67/71	140/218	3.384	1	0.06583
16	rs7187438	C	T	ALLELIC	67/71	140/218	3.654	1	0.05594
16	rs7187438	C	T	DOM	50/19	109/70	2.898	1	0.08872
16	rs7187438	C	T	REC	17/52	31/148	1.709	1	0.1911

16	rs1051771	C	G	GENO	0/6/61	1/23/151	1.217	2	0.5441
16	rs1051771	C	G	TREND	6/128	25/325	1.148	1	0.284
16	rs1051771	C	G	ALLELIC	6/128	25/325	1.148	1	0.2839
16	rs1051771	C	G	DOM	6/61	24/151	1.01	1	0.3148
16	rs1051771	C	G	REC	0/67	1/174	0.384	1	0.5352
17	rs196929	T	C	GENO	10/23/31	17/54/85	1.164	2	0.5587
17	rs196929	T	C	TREND	43/85	88/224	1.084	1	0.2978
17	rs196929	T	C	ALLELIC	43/85	88/224	1.261	1	0.2616
17	rs196929	T	C	DOM	33/31	71/85	0.6663	1	0.4143
17	rs196929	T	C	REC	10/54	17/139	0.9421	1	0.3317
17	rs16947425	A	C	GENO	4/20/43	3/39/122	4.072	2	0.1305
17	rs16947425	A	C	TREND	28/106	45/283	3.54	1	0.0599
17	rs16947425	A	C	ALLELIC	28/106	45/283	3.682	1	0.05499
17	rs16947425	A	C	DOM	24/43	42/122	2.43	1	0.1190
17	rs16947425	A	C	REC	4/63	3/161	2.776	1	0.0957
17	rs196950	T	C	GENO	15/27/29	25/56/92	3.387	2	0.1839
17	rs196950	T	C	TREND	57/85	106/240	3.31	1	0.06887
17	rs196950	T	C	ALLELIC	57/85	106/240	4.089	1	0.04316
17	rs196950	T	C	DOM	42/29	81/92	3.064	1	0.08007
17	rs196950	T	C	REC	15/56	25/148	1.637	1	0.2008
17	rs1874087	T	C	GENO	24/28/20	40/74/54	2.341	2	0.3102
17	rs1874087	T	C	TREND	76/68	154/182	1.696	1	0.1928
17	rs1874087	T	C	ALLELIC	76/68	154/182	1.948	1	0.1628
17	rs1874087	T	C	DOM	52/20	114/54	0.4503	1	0.5022
17	rs1874087	T	C	REC	24/48	40/128	2.338	1	0.1263
17	rs11655020	A	G	GENO	7/49/17	20/103/58	2.363	2	0.3069
17	rs11655020	A	G	TREND	63/83	143/219	0.7568	1	0.3843
17	rs11655020	A	G	ALLELIC	63/83	143/219	0.5743	1	0.4486
17	rs11655020	A	G	DOM	56/17	123/58	1.917	1	0.1662
17	rs11655020	A	G	REC	7/66	20/161	0.1168	1	0.7325
17	rs4255830	G	A	GENO	16/32/20	43/86/46	0.2419	2	0.8861
17	rs4255830	G	A	TREND	64/72	172/178	0.1657	1	0.684
17	rs4255830	G	A	ALLELIC	64/72	172/178	0.1703	1	0.6799
17	rs4255830	G	A	DOM	48/20	129/46	0.2419	1	0.6228
17	rs4255830	G	A	REC	16/52	43/132	0.02892	1	0.865
17	rs4396582	G	A	GENO	19/35/18	48/76/51	0.6386	2	0.7266
17	rs4396582	G	A	TREND	73/71	172/178	0.08923	1	0.7652
17	rs4396582	G	A	ALLELIC	73/71	172/178	0.09825	1	0.7539
17	rs4396582	G	A	DOM	54/18	124/51	0.4349	1	0.5096
17	rs4396582	G	A	REC	19/53	48/127	0.02789	1	0.8674
17	rs11651724	A	G	GENO	0/5/23	10/42/52	9.848	2	0.00727
17	rs11651724	A	G	TREND	5/51	62/146	9.582	1	0.001965
17	rs11651724	A	G	ALLELIC	5/51	62/146	10.16	1	0.001438
17	rs11651724	A	G	DOM	5/23	52/52	9.29	1	0.0023
17	rs11651724	A	G	REC	0/28	10/94	2.913	1	0.0878
17	rs2289764	C	T	GENO	10/20/38	18/53/92	0.68	2	0.7118
17	rs2289764	C	T	TREND	40/96	89/237	0.1749	1	0.6758
17	rs2289764	C	T	ALLELIC	40/96	89/237	0.2125	1	0.6448
17	rs2289764	C	T	DOM	30/38	71/92	0.006101	1	0.9377
17	rs2289764	C	T	REC	10/58	18/145	0.6044	1	0.4369
17	rs1012117	A	G	GENO	5/26/30	17/73/82	0.1573	2	0.9244
17	rs1012117	A	G	TREND	36/86	107/237	0.1078	1	0.7427
17	rs1012117	A	G	ALLELIC	36/86	107/237	0.1079	1	0.7425
17	rs1012117	A	G	DOM	31/30	90/82	0.04091	1	0.8397
17	rs1012117	A	G	REC	5/56	17/155	0.1499	1	0.6987
22	rs2097461	C	T	GENO	9/32/31	30/81/77	0.4922	2	0.7818
22	rs2097461	C	T	TREND	50/94	141/235	0.3246	1	0.5688
22	rs2097461	C	T	ALLELIC	50/94	141/235	0.3457	1	0.5565
22	rs2097461	C	T	DOM	41/31	111/77	0.09437	1	0.7587
22	rs2097461	C	T	REC	9/63	30/158	0.4881	1	0.4848
22	rs2239815	C	T	GENO	14/29/27	32/72/70	0.1031	2	0.9497
22	rs2239815	C	T	TREND	57/83	136/212	0.09827	1	0.7539
22	rs2239815	C	T	ALLELIC	57/83	136/212	0.1115	1	0.7385

22	rs2239815	C	T	DOM	43/27	104/70	0.05733	1	0.8108
22	rs2239815	C	T	REC	14/56	32/142	0.0845	1	0.7713

Table 13. Dental Registry and DNA Repository (DRDR) codes and their respective Phecodes.

DRDR Description	DRDR Code	Phecode	PheWAS Description
Primary Caries	DC001	521.1	caries
Primary Caries - 1 surface	DC001A	521.1	caries
Primary Caries - 2 surface	DC001B	521.1	caries
Primary Caries - 3 surface	DC001C	521.1	caries
Primary Caries - 4 surface	DC001D	521.1	caries
Primary Caries - 5 surface	DC001E	521.1	caries
Secondary Caries	DC002	521.1	caries
Secondary Caries - 1 surface	DC002A	521.1	caries
Secondary Caries - 2 surface	DC002B	521.1	caries
Secondary Caries - 3 surface	DC002C	521.1	caries
Secondary Caries - 4 surface	DC002D	521.1	caries
Secondary Caries - 5 surface	DC002E	521.1	caries
Gingivitis	DC003	523.1	Gingivitis
Mild Periodontitis	DC004	523	Gingival and periodontal diseases
Chronic Periodontitis	DC005	523.32	Chronic periodontitis
Aggressive Periodontitis	DC006	523.31	Acute periodontitis
Periodontal Abscess	DC007	523.32	Gingival and periodontal diseases
Endodontic abscess	DC008	523.31	Diseases of pulp and periapical tissues
Impacted tooth	DC009	520	Disorders of tooth development
Bruxism	DC010	327.7	Sleep related movement disorders
Malocclusion	DC011	524.3	Anomalies of tooth position/malocclusion
Abrasion	DC012	521	Dental erosion, abrasion and attrition
Pulpitis	DC013	522	Diseases of pulp and periapical tissues
Agenesis	DC015	520.2	Disturbances in tooth eruption
Prognathism	DC016	526.3	Anomalies of jaw size/symmetry
Retrognathism	DC017	526.3	Anomalies of jaw size/symmetry

TMJ Disorder	DC018	526.4	Temporomandibular joint disorders
Macrodontia	DC021	520	Disorders of tooth development
Microdontia	DC022	520	Disorders of tooth development
Taurodontism	DC023	520	Disorders of tooth development
Internal resorption	DC025	521	Diseases of hard tissues of teeth
External resorption	DC026	521	Diseases of hard tissues of teeth
Ameloblastoma	DC027	526	Diseases of the jaws
Mucous retention cyst	DC029	526.1	Cysts of the jaws
Stomatitis	DC030	528.1	Stomatitis and mucositis
Xerostomia	DC031	527.7	Disturbance of salivary secretion
Gingival recession	DC032	523.1	Gingivitis
Missing	DC033	525.1	Loss of teeth or edentulism
Dental fracture	DC034	525	Tooth fracture
Residual tooth root	DC035	525	Tooth fracture
Periapical lesion	DC036	522.5	Periapical abscess
Slight dental mobility	DC037	523	Gingival and periodontal diseases
Severe dental mobility	DC038	523.3	Periodontitis (acute or chronic)
Horizontal bone resorption	DC039	523.3	Periodontitis (acute or chronic)
Vertical bone resorption	DC040	523.3	Periodontitis (acute or chronic)
Tooth ankylosis	DC041	520.2	Disturbances in tooth eruption
Attrition	DC042	521	Dental erosion, abrasion and attrition
Decalcification	DC043	521.1	Dental caries
Partial edentulism	DC044	525.1	Loss of teeth or edentulism
Total edentulism	DC045	525.1	Loss of teeth or edentulism
Leukoedema	DC046	528.6	Leukoplakia of oral mucosa
Bilateral Linea Alba	DC047	528.6	Leukoplakia of oral mucosa
Unilateral Linea Alba	DC048	528.6	Leukoplakia of oral mucosa
Microglossia	DC049	529	Diseases of the tongue
Macroglossia	DC050	529	Diseases of the tongue
Fordyce granules	DC051	706	Diseases of sebaceous glands
Dry/chapped	DC052	528.5	Diseases of lips
Coated	DC053	529	Diseases of the tongue

Pillars/Trigone	DC054	695.8	Other specified erythematous conditions
Fissured	DC055	529	Diseases of the tongue
Ulcers	DC057	528.11	Ulcerative stomatitis & mucositis
Torus maxillary	DC058	526.8	Exostosis of jaw
Torus mandibular	DC061	526.8	Exostosis of jaw
Gingival hyperplasia	DC063	526.3	Gingivitis
Cyst	DC064	526.1	Cysts of the jaws
Root resorption	DC066	521	Diseases of hard tissues of teeth
Extracted for orthodontic reasons	DC069	525.1	Loss of teeth or edentulism
Extracted due to caries	DC069A	525.1	Loss of teeth or edentulism
Extracted due to periodontitis	DC069B	525.1	Loss of teeth or edentulism
Ankyloglossia	DC071	529	Diseases of the tongue
Erosion	DC074	521	Diseases of hard tissues of teeth
Geographic tongue	DC077	529.1	Glossitis
Supernumerary tooth	DC078	520	Disorders of tooth development
Leukoplakia	DC080	528.6	Leukoplakia of oral mucosa
Abfraction	DC081	521	Diseases of hard tissues of teeth
Oral cancer	DC087	145	Cancer of mouth
White line on buccal	DC089	528.6	Leukoplakia of oral mucosa
Unerupted	DC090	520.2	Disturbances in tooth eruption
Temporary Filling	DC091	525	Other diseases of the teeth and supporting structures
Cleft, unspecified	DC094	749	Congenital anomalies of face and neck
Cleft	DC095	749	Congenital anomalies of face and neck
Cleft, unilateral	DC097	749	Congenital anomalies of face and neck
Cleft, bilateral	DC098	749	Congenital anomalies of face and neck
Lingual varicosities	DC100	454	Varicose veins
Incipient Caries	DC111	521.1	Dental caries
Lip Chewing	DC113	528.5	Diseases of lips
Tonsils Red	DC116	474.2	Chronic tonsillitis and adenoiditis
Tonsils Swelling	DC117	474.2	Chronic tonsillitis and adenoiditis
Asymmetric Tonsils	DC118	474.2	Chronic tonsillitis and adenoiditis

Tonsils Brodsky	DC119	474.2	Chronic tonsillitis and adenoiditis
Brodsky 2	DC120	474.2	Chronic tonsillitis and adenoiditis
Rampant Caries	DC122	521.1	Dental caries
Hypodontia	DC123	520	Disorders of tooth development
Calculus	DC124	523	Gingival and periodontal diseases
Partial Eruption	DC125	520.2	Disturbances in tooth eruption
Crowding	DC126	524.3	Anomalies of tooth position/malocclusion
Space	DC127	526.3	Anomalies of jaw size/symmetry
Shifted Mesially	DC128	526.3	Anomalies of jaw size/symmetry
Diastema	DC129	526.3	Anomalies of jaw size/symmetry
Fistula	DC133	522	Diseases of pulp and periapical tissues
Hemangioma	DC136	228	Hemangioma and lymphangioma, any site
Cervical Node	DC137	289.4	Lymphadenitis
Candidiasis	DC139	112	Candidiasis
Tongue Scalloped	DC142	529	Diseases of the tongue
Dry Eyes	DC144	375	Disorders of lacrimal system
Midline shift	DC146	524.3	Anomalies of tooth position/malocclusion
Physiologic Pigmentation on tongue	DC149	529	Diseases of the tongue
Occlusion 2	DC152	526.3	Anomalies of jaw size/symmetry
Occlusion 3	DC153	526.3	Anomalies of jaw size/symmetry
Endodontic treatment - anterior	D3310	522	Diseases of pulp and periapical tissues
Endodontic treatment - bicuspid	D3320	522	Diseases of pulp and periapical tissues
Endodontic treatment - molar	D3330	522	Diseases of pulp and periapical tissues
Hyperkeratosis tongue	DC150	529	Diseases of the tongue
Fibroma	DC138	528	Diseases of the oral soft tissues

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