FAMILIAL CORRELATION IN DENTAL CARIES AND PERIODONTAL DISEASE: INDICATORS AND RISK FACTORS

by

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Jennifer Rose Moeller, M.S.

University of Pittsburgh, 2009

Research Aims: Many studies have identified an association between cardiovascular disease and periodontal disease. Awareness is growing that oral health is important in an individual's general health. There is evidence suggesting that oral conditions, such as dental caries and periodontal disease, are due to bacteria contained in plaque and treatable, possibly preventable conditions. The aims of this study are 1) determine if there is a familial correlation in the ability to host supragingival and subgingival bacteria, 2) determine familiality in the development of dental caries and periodontal disease, and 3) if there is a familial correlation, propose modifications to the oral health hygiene standard of care that may influence the development of oral disease, which in turn may lower the risk of developing cardiovascular disease.

Methods: Data were obtained from the COHRA study (IRB #020773 and #0506048). Participants (n = 2,570) contacted the study coordinator and attended a clinic at which DNA samples were obtained, dental examinations were performed, and questionnaires were completed. FCOR, a S.A.G.E. statistical program, was used to analyze the data and determine the familial correlation between relative pair-types.

Results: The influences of environment and genetic make-up in regards to oral health, specifically the ability to host bacteria and the development of dental caries and periodontal disease, are complex. The correlations of all pair-types were similar and likely overlap when the standard error is considered.

Conclusion: Results suggested that there was no strong evidence of a genetic influence on the ability to host supragingival or subgingival bacteria or the development of dental caries or periodontal disease. However, the amount of influence environment and genetic factors have in the development of oral disease remains unclear.

Public Health Significance: The relationship between cardiovascular disease and periodontal disease is not understood. A continuated attempt to understand the components of oral disease status and its influence on cardiovascular disease may provide an avenue by which to decrease an individual's risk to develop cardiovascular disease.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

PREFACE

I would like to express my gratitude to Dr. Mary Marazita, who has provided me with an abundance of opportunity and freedom to explore my interests while at the University of Pittsburgh. She has been incredibly supportive and encouraging throughout the thesis process.

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Please note the results of this paper were obtained by using the software package S.A.G.E., which is supported by a U.S. Public Health Service Resource Grant (RR03655) from the National Center for Research Resources.

Soli Deo Gloria! All Glory to God!

Without Him, I cannot succeed. With Him, I cannot fail!

1.0 BACKGROUND AND SIGNIFICANCE

Oral health has been shown to have significant importance to the overall health of an individual. The mouth can serve as a window and allow us to examine what diseases are already occurring in the body, such as HIV/AIDS and diabetes mellitus, or what a person may be at risk for in the future, such as stroke or heart disease [1]. The presence of bacteria-containing subgingival plaque, which is associated with periodontal disease, has been correlated with an increased risk of cardiovascular disease [2]. Infection was thought to be a risk factor for cardiovascular disease over 100 years ago [3], but scientific investigation into such an idea only began a little over 15 years ago [4]. There is still a debate as to the type of association between periodontal disease and cardiovascular disease: causal or correlative. Identification, evidence, and classification of an association are complicated by the complexity of quantifying measurements for each of the diseases. The lack of standard definitions of exposures, periodontal disease, and outcomes has also added to the difficulty in assessing the type of association [3]. Many studies support and provide evidence that there is at least some association between periodontal disease and cardiovascular disease, though the nature is still unclear. The association appears to be a positive correlation; an increase in the amount of plaque-containing bacteria increases the risk of cardiovascular disease.

Many advances have been made in the area of oral health and oral hygiene. In the 1920s, observations of plaque growth and dental decay lead to the recommendation of tooth brushing

and annual or semiannual cleanings by a dentist in the attempt to reduce plaque growth [5]. It was thought that plaque itself was the cause of dental decay, known as the non-specific plaque hypothesis. In the 1960s, fluoride was added to toothpaste in an attempt to stop the oral decay that was being observed. In 1976, the specific-plaque hypothesis was proposed by Loesche [6], who asserted that S*treptococci mutans* played a unique role in dental decay. Today, we understand that dental caries, periodontal infections, and tongue conditions are associated with unique plaque containing specific bacteria, such as *Porphyromonas gingivalis* [7], and that these bacteria may be involved in other systemic conditions.

Subgingival plaque, which is associated with periodontal disease [5; 8] and an increased risk for cardiovascular disease, can be identified by a professional and controlled through treatment. Supragingival plaque, which is associated with the development of dental caries and tooth decay, may be involved in the development of subgingival plaque. This plaque can also be controlled through treatment and thus, reduce the risk of dental caries, tooth decay, and subgingival plaque [5].

It is clear that many complex diseases, including periodontal disease, have a genetic basis [9]. Oral health has seen anecdotal evidence of a genetic basis. Multiple patients report, "Bad gums run in my family" or "My mother had chalky teeth too" [10]. Periodontal disease has also been observed to aggregate within families [9]. There are other factors involved, such as environment, microbes, and behavior that can also be transmitted through families from parent to child. Identifying the familiality in the presence and levels of supragingival and subgingival bacteria-hosting plaque may provide a first step in treatment and early intervention protocols for systemic disease. It would aid in developing recommendations for the appropriate standard of

care to individuals and their families. These interventions may benefit a patient through both their oral health and their cardiovascular health.

1.1 DENTAL CARIES

Dental caries is one of the most common oral diseases [10] and is caused by the bacterial fermentation of sugars and other dietary carbohydrates which lead to the decay of tooth mineral [5]. Bacteria that are a part of the normal human flora of the tooth respond to the amount of dietary sugars being introduced and begin to grow and expand on the tooth surface in which they cover. As the bacteria metabolize the sugars, the plaque becomes more acidic, causing the tooth to become the buffer and release calcium and phosphate ions. If these minerals are not replaced, a loss of tooth substance occurs and a white spot lesion forms. This is the beginning stage of dental caries. As the condition progresses, the bacteria penetrate the enamel crystalline and the underlying dentine. Cavitation is a late event in the dental caries process.

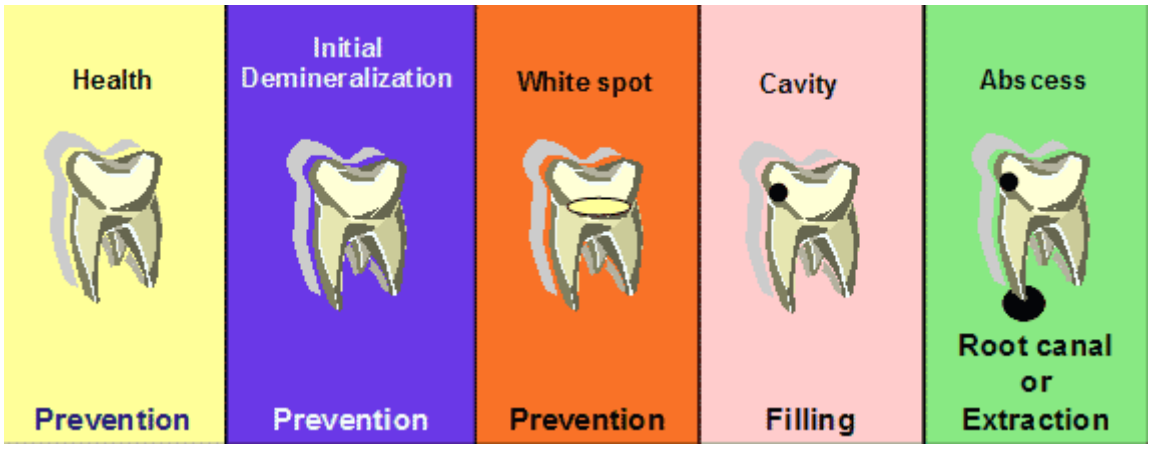

Figure 1 Stages of the development of dental caries [11]

Currently, dental caries are seen as multifactorial based upon host, microbial, and environmental factors [10]. It is thought that influences of all of these components play a role in

the development of dental caries and decay. Recently, studies have suggested that there is approximately a 50% genetic contribution to the development of dental caries [10]. As shown in the figure below, genetic contributions are not being included in the multifactorial model as of yet.

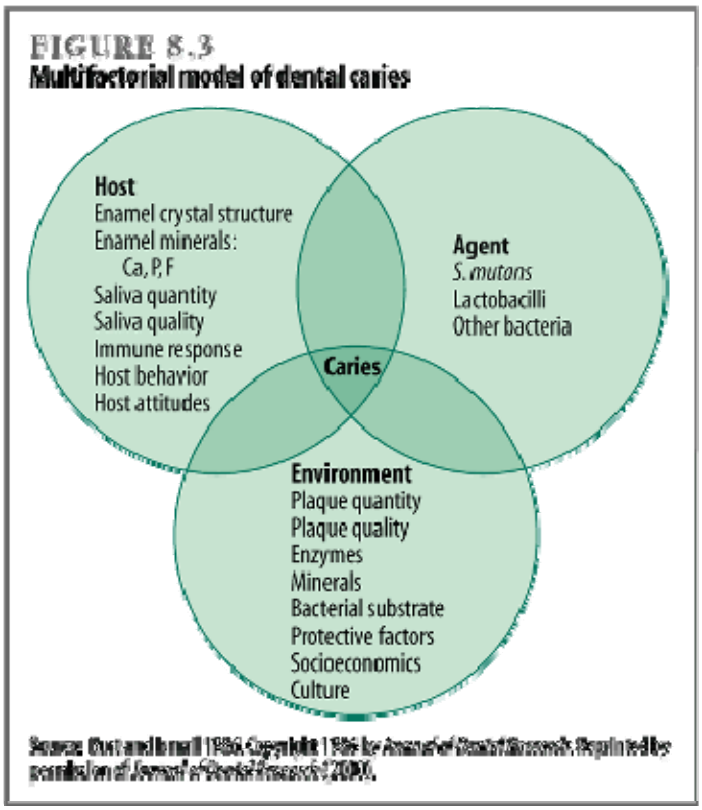

Figure 2 Dental caries as a multifactorial condition [12]

1.1.1 Bacteria involved in dental caries

Mutans streptococci include the bacteria *S mutans* and *Streptococcus sobrinus*. The majority of the time, these bacteria are referred to in tandem and are identified as *mutans streptococci*.

S mutans were identified as a cause for dental caries using rodent models in the 1960s [10]. The association to human dental decay was uncertain given that *mutans streptococci* are dental pathogens typically found on the human teeth.

1.2 PERIODONTAL DISEASE

Periodontitis is a widespread condition due to a chronic bacterial infection [7; 13; 14]. These bacteria invoke a chronic inflammatory response that results in the destruction of connective tissue and bone of the dentition [15]. By the age of 12 years, 40% of the population is found to have moderate periodontitis. Of those over 65 years of age, 80% are found to have moderate periodontal destruction [13]. Many of the signs of periodontal disease include tooth loss, gingivitis, periodontal bleeding and inflammation, excess plaque, infection, decay, tooth mobility, gum recession, and bone loss [16]. Not all individuals with periodontal disease will show warning signs or symptoms of the disease [17].

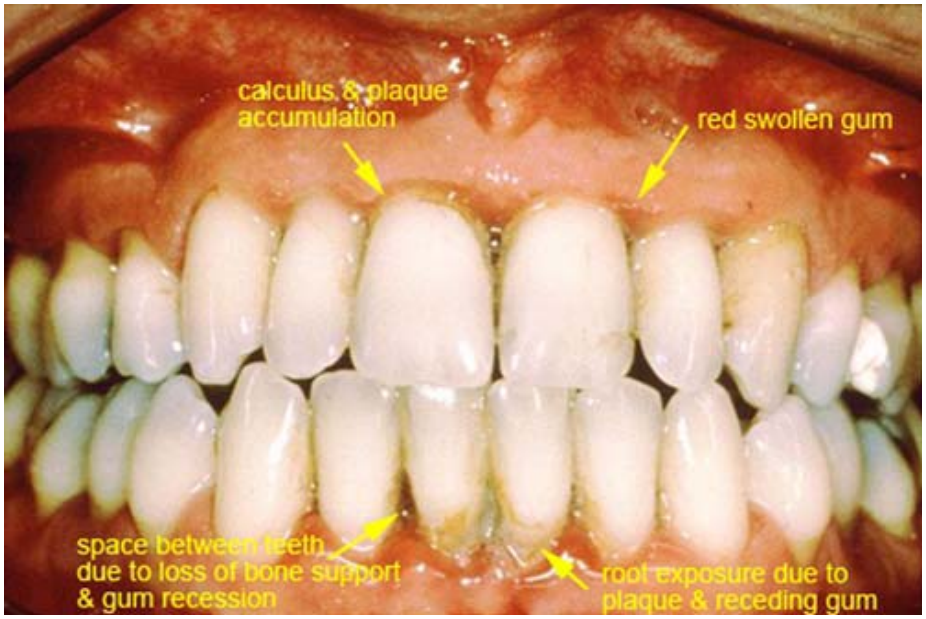

Figure 3 Common signs of periodontal disease [16]

Periodontal disease has been found to be associated with multiple systemic conditions, such as airway obstruction [15], cardiovascular disease [3; 4; 7; 14], and diabetes [7]. Low birthweight of babies has also been associated with the presence of periodontal disease in the mother [14]. The

relationship between systemic conditions and periodontal disease, and their pathways are still under investigation [7].

Evidence suggests that a majority of the diseases seen today have a genetic basis, including periodontal disease [9]. The development of periodontal disease is under many influences, such as microbial, environmental, behavioral and genetic [9; 14]. In a study by Yang et. al, 18 – 48 month old daughters of mothers with periodontitis have 5.8 times the odds for *Bacteroides forsythus*, a bacterial species associated with periodontal disease, than those age matched daughters of mother without periodontitis [18]. This study supports the thought that there is likely to be a familial correlation in the ability to host oral bacteria associated with periodontal disease. Kinane et. al. has suggested that aggressive periodontal disease is inherited in an autosomal dominant pattern with reduced penetrance [9]. This indicates a near 50% risk of developing the disease for first-degree relatives of those with periodontal disease. Hart et. al. suggested through a literature review that while microbial factors are required for periodontal disease to develop, they do not predict the severity or even the presence of disease [14]. Systemic factors also affect the disease risk and progression by their effects on the immune and inflammatory response of the individual [7]. It is clear that the response put forth by the body is influenced by the obviously complex interactions between all of these components [7; 14]. It is also clear that these components are broadly transmissible through families.

Many studies have shown the aggregation of periodontal disease through families, suggesting a genetic component being transmitted [9; 13]. The underlying component may be due to changes on the DNA level, such as a nucleotide change [9]. This change is known as a genetic polymorphism. A genetic polymorphism may alter the function of the gene or its product, but is less disruptive than a mutation, a harmful change. The product may be changed slightly, which

alters its interactions with other genes, gene products, environment, and body responses to predispose or protect an individual. Genetic polymorphisms can be passed through the family from generation to generation and may provide some explanation to the familial aggregation seen.

1.2.1 Bacteria involved in periodontal disease

Subgingival bacteria initially colonize in the supragingival plaque [5]. These bacteria become anaerobic and move beneath the gingival margin where there is a lower pressure of oxygen tensions. Certain bacteria detected within the mouth have been reported to be involved in the progression of periodontitis. In a study by Yang et. al, *Bacteroides forsythus* (now known as *Tannerella forsythensis*) was found to be significant associated with the progression of periodontal disease, whereas *Porphyromonas gingivalis*, *Actinobacillus actinomycetemcomitans* were not [18]. Tuite-McDonnell et. al. presented results indicating that children of parents with colonized *Porphyromaonas gingivalis*, which is associated with periodontitis indicators such as deep pockets and loss of attachment, are at a greater risk of colonizing *P. gingivalis* [13]. Potentially, the presence of *Porphyromonas gingivalis, Treponema denticola, Tannerella forsythensis (Bacteriodes forsythus)* in combination with genetic markers may be able to predict periodontal disease severity [19].

1.3 CARDIOVASCULAR DISEASE

According to the American Heart Association, 80 million individuals were known to have one or more forms of cardiovascular disease in the year 2006. Cardiovascular disease was also the reported final cause of death in 1 out of 2.8 deaths in 2005 [20]. In developed countries, coronary heart disease is the leading cause of death and morbidity, killing more than 7 million people worldwide per year [16]. Coronary artery disease is the major cause of premature death among men [7]. Cardiovascular disease has great implications for an individual's quality of life and the financial responsibilities of an individual and society [14]. The economic cost of cardiovascular disease and stroke in 2008 was $475.3 billion, which includes costs such as physicians and hospitals and loss of productivity. The cost is thought to be even greater after inclusion of the immeasurable costs of suffering and the loss of human lives [20].

There are many known risk factors for heart disease. Some risk factors can be changed or eliminated to adjust an individual's risk of heart disease such as smoking, high blood pressure, high blood cholesterol, diabetes, being overweight or obese, poor diet and exercise [21]. Some risk factors, however, cannot be changed and include age, gender, and family history [22]. Oral health is being acknowledged more commonly as a risk factor for cardiovascular disease [1-5; 7; 16; 23-25].

The genetic basis for cardiovascular disease has been difficult to study given the variable expressivity and complex nature of the disease itself [14]. This has caused a lack in a complete understanding of the disease. However, the ability to study such complex diseases is changing and may produce a new understanding and ability to intervene with these conditions.

1.4 ORAL HEALTH AND CARDIOVASCULAR HEALTH

Chronic infection is recognized as being a potential instigator in the development of systemic diseases, including cardiovascular disease [7; 16; 19; 26]. In individuals under the age of 50 years, missing teeth due to periodontal inflammation was associated with multiple medical conditions, as seen in Table 1 [5]. Periodontal bone loss has been associated with increased odds of coronary artery disease (1.5), fatal coronary heart disease (1.9), and stroke (2.8) relative to appropriate comparison groups. Humphrey et al. showed that periodontal disease was associated with a 24-35% increase in risk for coronary heart disease [16].

Table 1 Medical conditions in which dental infections may be contributory [5]

Medical condition	**Dental risk indicator**
Preterm births	Periodontal infections (gram-negative anaerobes)
Cerebral vascular accident	Periodontal infections (gram-negative anaerobes)
Coronary artery disease	Periodontal infections (gram-negative anaerobes); Tooth loss
Diabetes	Periodontal infections (gram-negative anaerobes)
Alzheimer's disease	Tooth loss before age 35 years

Continued investigation into the causality and pathways between periodontal disease and cardiovascular disease is necessary. The importance of other microbes present [26] or other systemic conditions identified in the individual [7] is unclear. The interactions between oral infection, cardiovascular disease, genetic influences and body responses are also unclear and require more investigation. In 2004, Janket et. al. presented a diagram of potential pathways associating oral health with systemic health [27], which can be found below.

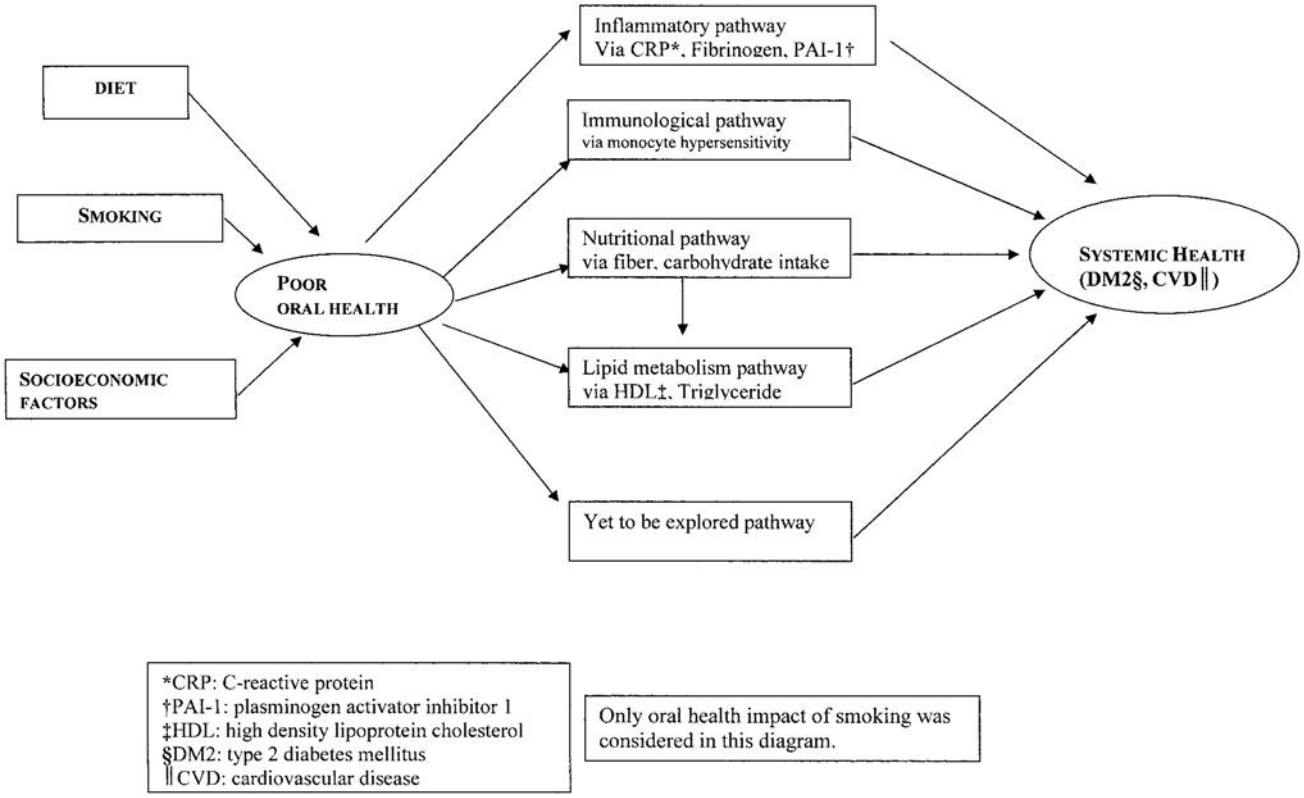

Figure 4 Hypothetical diagram of pathways linking oral and cardiovascular health [27]

1.4.1 Bacteria and its association with oral health and cardiovascular health

Porphyromonas gingivalis is bacteria specific to the oral cavity [27]. It has been linked with indicators of periodontal disease, such as deep pockets and attachment loss [13; 28]. Many studies have found specific antibodies of that bacteria in atherosclerotic plaques of patients with periodontal disease [27]. The detection of those bacteria in that location suggests that periodontal disease may be linked with cardiovascular disease. Other studies have shown that these bacteria have the ability to invade endothelial cells *in vitro* [7]. It is thought that this invasion may be an initiating factor or alter the progression of arthrosclerosis, a factor in cardiovascular disease.

1.5 CURRENT TREATMENT OPTIONS FOR DENTAL CARIES AND PERIODONTAL DISEASE

Even in the presence of oral disease, a microbial sample is rarely taken and confirmed [5]. The knowledge of the underlying microbial infection would not change the treatment the patient receives because treatment is determined in response to the symptoms presented by the patient. However, research has shown evidence that dental caries and periodontal disease have a genetic basis. Therefore, some individuals may be predisposed or have a greater likelihood to host these bacteria leading to poor oral health. Current treatment options do not take genetic variations and their implications into account, but are similar for all individuals.

The current paradigm of disease treatment is not designed to account for the multitude of genetic information known to impact our oral health [14]. It may be time for another adjustment in our view and paradigm of oral health and disease treatment. Knowledge of a genetic predisposition and/or a family correlation to host bacteria associated with dental caries and periodontal disease could allow for prophylactic treatment options for patients and their families. Not only could these treatments include prophylactic screening and treatment for dental caries and periodontal disease, but research has suggested treatment to reduce or prevent the presence of oral bacteria may have results impacting their cardiovascular health as well [2; 7; 24; 26].

Currently, the standard of care is to brush with fluoride toothpaste twice a day, floss once a day, eat a balanced diet with limited snacking, and attend regularly scheduled visits with a dentist for an examination and cleaning [8]. Fluoride has been added to the drinking water of many cities and to the toothpaste available to consumers. Fluoride has an anti-microbial effect at acidic pH levels, allowing the tooth to dissolve and decay at a slower rate than without fluoride [5]. Periodontal disease can be treated by removing the debris from the tooth surface and with a

systemic antibiotic [5]. Seeing a dentist regularly allows early signs of periodontal disease to be detected so that a patient may begin treatment in the early stages. Some of the signs that may be observed are: tooth loss, gingivitis, periodontal bleeding, gum inflammation, excess plaque, infection, decay, tooth mobility, gum recession, and bone loss [16]. It is possible, however, to not exhibit warning signs of disease [17]. For these individuals and those who have a greater likelihood to better host these bacteria, a new standard of care should be investigated.

2.0 AIMS OF THE STUDY

2.1 AIM 1

Determine if the ability to host supragingival bacteria (*S. mutans*) and subgingival bacteria (*Porphyromonas gingivalis*, *Treponema denticola*, and *Tannerella forsythensis* (formally known as *Bacteriodes forsythus*)) within oral plaque has a genetic and/or familial component.

2.1.1 AIM 1A

Determine the family correlation between family members based on semi-quantitative measures of microbial infection using data from the Dentocult® test (supragingival plaque samples, caries related organisms) and the BANA™ test (subgingival plaque samples, periodontal disease-related organisms).

2.2 AIM 2

Investigate familiality in the development of dental caries and periodontal disease.

2.2.1 AIM 2A

Determine the family correlation between family members based on caries indicators (DMFT, DMFS) and periodontal disease indicators (probing depth, bleeding on probing).

2.3 AIM 3

If the family correlations are consistent with a significant genetic component, investigate possible modifications to current dental health recommendations.

3.0 METHODS AND PROCEDURES

The COHRA study, from which these data were obtained, was initiated through a collaboration between Dr. Mary Marazita and Dr. Robert Weyant and approved by the Institutional Board of Review (Appendix B and Appendix D). The data used in this research was collected from 2002 until present.

3.1 PROTOCOL SUMMARY

Families with at least one child between the ages of 1 and 18 years of age living in West Virginia (80% of the participants) and Pennsylvania (20% of the participants) were invited to participate in the study through IRB-approved fliers, radio and television advertisements, and talks to schools and organizations (Appendix B). If a family was interested in participating in the study, the prospective participant telephoned the study coordinator. At that time, the primary care giver was identified as the index case, the research protocol was explained, and a screening interview was given to determine eligibility. If the family fulfilled the eligibility criteria, the family and family members were given an ID number to preserve confidentiality. Adults and children (Appendix B) in the family were invited to participate. After the screening interview form was completed and eligibility was determined, an appointment was made for the family to attend the clinic and an information packet containing a welcome letter, a sample consent form, and vial to

collect a sample of the household water was provided. At the time that they came in to the clinic, the family was consented. Parents consented for themselves and their children. The antibiotic screening form and the protocol were reviewed with the family to answer any additional questions. At this time, family members were rotated through the research stations (i.e. questionnaires, dental examination, physical examination, and sample collection). At the end of the procedure (approximately 4 hours), the participants were reimbursed $25 for each visit. Children were reimbursed with a gift card made out in their name to avoid parental coercion to participate. Follow-up appointments occur every 2 years for a total of 3 to 4 visits.

3.2 INITIAL CONTACT OF INTEREST

Prior to the participant's first visit, they contacted a research coordinator by telephone and discussed the study protocol, study eligibility, and were given an ID number. During this conversation, the participant was asked questions from a screening survey regarding demographic information to determine eligibility.

3.2.1 Screening interview form

The screening survey focused on demographic information and was divided into four parts. Part 1 asked information regarding how the participant learned about the project, their age and gender, and their ethnicity. Part 2 obtained information regarding the participant's household situation. This included information such as where their home was located, how long they had lived at their home, how many individuals lived in the home with them, and how they were

related to those individuals. This section of the survey also asked how many total vehicles were owned by individuals in the home as well as the total yearly income of the household. Part 3 asked participants about the type of home in which they lived, if they owned or rented their home, and the types of utilities they had, such as gas heat versus electric heat.

The last section, part 4, was used to determine if a participant was to be excluded from the study through questions regarding a reduced ability to fight infection, artificial joint replacement, or need to take medication before a dental examination. If the participant answered "yes" or "suspects" to these questions, his/her case was reviewed by a select group of individuals at the Center for Craniofacial and Dental Genetics to determine if the individual was to be included in the study or if invasive sections of the dental examination were to be avoided. Those individuals who were found to have neurologic impairment, a severe physical or intellectual handicap, or psychosis were excluded from the study. In addition, households with an adult who required antibiotic pre-medication, but refused to take it, were excluded from the study. Children required to take antibiotic pre-medication for dental work were excluded from any invasive procedure that may cause bleeding.

3.3 VISIT 1

3.3.1 Station 1

3.3.1.1 Consent interview

Before any other part of the study protocol was started, the participants were consented. At this time the consent forms (Appendix A and Appendix C) were explained and signed. Each

individual participating in the study had to sign a consent form. The protocol was explained and reviewed and participant questions are answered.

3.3.1.2 Antibiotic Screening Form

The purpose of this screening form, reviewed at the time of scheduling the appointment, was to identify those that require antibiotic pre-medication, have an inhibited ability to fight infection, or are at risk to develop infection. These individuals were informed of the sections of the procedure that may have be to avoided if they refuse to adhere to the American Heart Association guidelines for pre-medication. They were also informed of the health risks associated with the antibiotic prophylaxes Amoxicillin and Clindamycin.

3.3.1.3 Collecting the household water sample

During the phone conversation to set up an appointment, each family was asked to retrieve a sample of their drinking water with the vial provided in the packet mailed to them. This sample is stored by an IRB approved protocol for later studies.

3.3.2 Station 2

At station 2, study participants were asked to fill out a set of self-report questionnaires in which they provided demographic information, oral health history, and pregnancy history, if applicable, in addition to other information. Each of these surveys focused on different aspects of the individual's life that may be applicable or related to their oral health. Some questionnaires were not given to children because they were not applicable or their information was gathered through the survey of the parent.

Table 2 Visit 1 Self-Report Questionnaires by Age Group

	Questionnaires	Adult (18 + years)	14 – 17 years	11 – 13 years
1	SF-36 Health Survey	**X**	**X**	**X**
2	DUSI-R (Screening Form)	**X**	**X**	**X***
	DUSI-R	**X**	**X***	
3	Fagerstrom Test for Nicotine Dependence	**X**	**X**	**X**
4	Fagerstrom Test for Smokeless Tobacco Use	**X**	**X**	**X**
5	Dental Fear and Anxiety Scale **	**X**	**X**	**X**
6	Oral Health Impact Profile	**X**	**X**	**X**
7	Perceived Stress Scale	**X**	**X**	**X**
8	Fatalism Scale	**X**	**X**	**X**
9	Health Locus of Control	**X**	**X**	**X**
10	Parental Supervision and Involvement	**X**	**X***	**X***
11	Family Assessment Measure (FAM)***	**X**	**X**	**X**
	Section 1. General Scale	**(X)**	**(X)**	**(X)**
	Section 2. Dyadic Relationship Scale	**(X)**	**(X)**	**(X)**
	Section 3. Self-Rating Scale	**(X)**	**(X)**	**(X)**
12	ISEL	**X**	**X***	
13	West Virginia Identity Scale (WVIS)†	**X**	**X**	
	Parental Report Questionnaire‡		**X**	**X**

*** Youth Version**

**** A simplified version of the Dental Fear and Anxiety Scale is collected on children aged 1 – 10. It is administered as a parental report form using the teleform system.**

***** The FAM has 3 sections to be filled out by participants aged 11 and older. In Section 1, each participant answers questions regarding their family in general. Section 3 is a self-rating scale. Section 2 assesses dyadic relationships within families. Each individual answers questions about specific relatives. Staff takes out the FAM query sheets and fills out the name of each individual. The relationships to be documented are as follows: 1) Parents fill out a FAM query sheet for each child. 2) Child (aged 11 – 18) fill out a FAM query sheet for each parent.**

† The WVIS is used only at the West Virginia field sites

‡ The Parental Report Questionnaire is filled out by parents on all children aged 1 – 18. The version for children aged 1 – 10 is abbreviated.

3.3.3 Station 3

At station 3, DNA collection via phlebotomy or Oragene™. A blood sample collection was attempted on each participant and was the preferred DNA sample collection method. Blood samples were not able to be obtained from all participants. Other methods of DNA sample collection were explained.

3.3.3.1 Priority 1: Blood collection

Blood was the preferred DNA sample and was considered to be first priority. A trained phlebotomist performed a venipuncture on participants aged 1 year and older and collected an 8 ml sample.

3.3.3.2 Priority 2: Saliva samples

Saliva samples were taken from those in whom blood was not retrieved. These individuals were able to spit. The sample was taken at least one hour after eating or drinking.

3.3.3.3 Priority 3: Cheek swab samples preserved in Oragene™

In the case where neither blood nor "spit" saliva were able to be collected, cheek swabs were used to obtain a DNA sample. Tips of the cheek swabs were preserved in Oragene™.

3.3.3.4 Priority 4: Mouthwash samples

Mouthwash buccal samples were taken only if all options above were not feasible. Mouthwash samples were taken at least an hour after eating or drinking. Participants spat mouthwash samples into a blue-topped conical tube.

3.3.4 Station 4

The Clinical Dental Screening, conducted by a dentist or dental hygienist and dental assistant, was performed at station 4. It included a dental screening and microbiological sample collections in which results were documented on the dental screening form and supplement form

(Appendix F and Appendix G). At the end of the screening, the study participant received a Clinical Findings Report filled out by the dentist or dental hygienist performing the screening.

As seen in Figure 5, certain procedures were deemed inappropriate or not applicable for children under a certain age. Sections of the dental screening exam were omitted depending upon the study participant's age.

8705

COHRA Dental Examination

Age >=18

COHRA

ELIGIBILITY CRITERIA

Exam	Age 1 to 6	Age 7 to 10	Ages 11-13 and 14-17	Age >=18
2.1. Blood samples	yes	yes	yes	yes
3.1. SUPRAginval plaque	yes	yes	yes	yes
3.1. tongue scraping	yes	yes	yes	yes
3.2. Stimulated saliva secretion rates	NO	yes	yes	yes
4.1. Soft tissue exam	yes	yes	yes	yes
4.2. Dentures assessment	yes	yes	yes	yes
4.3. Eligibility criteria	yes	yes	yes	yes
4.4. Bana Tongue scraping	yes	yes	yes	yes
4.4. BANA SUBgingival plaque	NO	*Yes if no need of prof	*Yes if no need of prof	yes
4.5. Papillary bleeding score	NO	*Yes if no need of prof	*Yes if no need of prof	yes
4.6. Periodontal screening	NO	NO	NO	yes
4.7. Maloccusion	NO	yes	yes	yes
4.8. Caries	yes	yes	yes	yes
4.9. Trauma	yes	yes	yes	yes
4.10. Throat swab	yes	yes	yes	yes
4.11. Clinical findings	yes	yes	yes	yes

* ONLY IF NO PRE-MED NEEDED

Figure 5 Eligibility criteria for dental screening exam procedures dependent upon age

3.3.4.1 Supragingival plaque sample and tongue scraping for microbiology culture & DNA analysis

Dentocult® SM Strip mutans is a test that is used to determine the presence of *mutans streptococci* in plaque [29]. Plaque was removed from different locations of the tooth (TestR, SupTestR and Plaq) and placed on the square-ended wand provided with the kit.

An additional sample at the same locations was collected in multicolored capped Eppendorf tubes.

Table 3 Supragingival plaque samples

Sample Number &	**Instrument & method to use to**	**Corresponding Dentocult® stick**
Type of Surface	**collect sample**	**region &/or Eppendorf tube**
Sample 1: Surfaces of intact	Swipe tooth surface with sterile	**"1" on Dentocult Strip &**
(sound) & caries-free enamel	**Stimudent**	**White Cap Eppendorf**
Sample 2: Surfaces of white	Obtain plaque by pooling	**"2" on Dentocult Strip &**
spot lesion	material with sterile Gracey	**Yellow Cap Eppendorf**
	1/2	
Sample 3: Surfaces of cavitated	Obtain plaque by pooling	**"3" on Dentocult Strip &**
initial enamel lesions	material with sterile Gracey	**Orange Cap Eppendorf**
	1/2	
Sample 4: Carious dentin from	Obtain plaque by pooling	**"4" on Dentocult Strip &**
deep dentinal lesions	material with sterile Gracey	**Red Cap Eppendorf**
	1/2	
Sample 5: Tongue scraping	Use 1 Stimudent to scrape the	**Violet Cap Eppendorf (do not**
	tongue dorsum	collect on Dentocult strip)

3.3.4.2 Stimulated saliva secretion rate

The stimulated saliva collected from this procedure will be used in the *Mutans Streptococci* Test, Saliva Secretion Flow Rate, and Salivary Cotinine.

The individual was asked to chew on a piece of plan wax for one minute. After that time, they were asked to remove the wax from their mouth and the excess saliva was used for the salivary cotinine test. The round-ended wand provided in the kit was placed on their tongue ten times to identify *mutans streptococci*. The two wands were then snapped together and placed in the incubation broth.

The study participant performed the saliva secretion flow rate test by allow saliva to secret from their mouth and into a conical tube for three minutes.

3.3.4.3 Soft tissue exam

The dentist or dental hygienist visually inspected the mouth of the participant and documented all positive finding. A box labeled "Other Diagnosis Description" was provided for those findings that did not fit in to those types provided on the document.

3.3.4.4 Dentures assessment

The dentures of the study participants, if applicable, were examined. The type and location of the dentures were located on the examination form.

3.3.4.5 Eligibility criteria for edentulous patients

At this point in the dental exam, participants were determined to be completely edentulous, indicating that there were some sections of the dental exam that were not applicable to them, or not completely edentulous. Only a BANA™ tongue sample and the throat swab were obtained from those who were completely edentulous.

3.3.4.6 BANA™ plaque and tongue scraping; subgingival plaque for microbial DNA

Plaque samples from the mesio-buccal surfaces of four reference teeth were obtained from study participants. Each tooth was sampled twice. The reference teeth selected were the first molars on the maxilla (#3, 14) (Btest03 and Btest14) and mandible (#19, 30) (Btest19 and Btest30) (Figure 2). One sample from each sample site was placed on a BANA-Zyme™ test strip and then placed into the provided incubator. The other sample from each sample site was placed in green-topped Eppendorf tubes.

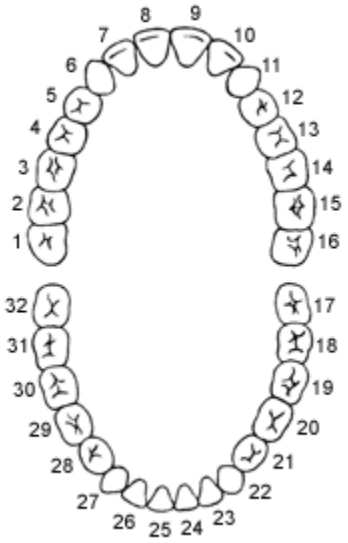

Figure 6 American numbering system of permanent teeth

A tongue scraping (TungRes) using a Stimudent was also performed to obtain a sample of the bacteria culture. This sample was placed on a BANA-Zyme™ test strip and then placed into the provided incubator.

Measurements of deep pockets in the gums (PSR03, PSR14, PSR19, PSR30), induction of bleeding with probing (BL03, BL14, BL19, BL30) and recession (REC03, RES14, RES19, RES30) (Periodontal Screening Record) were performed on each participant at each reference tooth used in the subgingival plaque sample collection.

3.3.4.7 Papillary bleeding score

A Stimudent was placed between each tooth for the count of 15 seconds. After 15 seconds, the Stimudent was removed and an assessment of the gingival (bleeding, redness and irritation) was made and documented in the examination packet.

Table 4 Loesche Papillary Bleeding Index

Papillary Bleeding Index (PBI) Loesche	Result of Stimudent Insertion
0	Healthy gingival tissue; no bleeding upon insertion of Stimudent interproximally.
1	Edematous, reddened gingival tissue; no bleeding upon insertion of Stimudent interproximally.
2	Bleeding without flow along gingival margin upon insertion of Stimudent interproximally.
3	Bleeding with flow along gingival margin upon insertion of Stimudent interproximally.
4	Copious bleeding upon insertion of Stimudent interproximally.
5	Severe inflammation, marked redness and edema; tendency to spontaneous bleeding.
9	One of the pair of teeth is missing.

3.3.4.8 Periodontal screening record (PSR) in subjects > 17 years old

Each tooth was examined individually using a periodontal probe for deep pockets (S1, S2, S3, S4, S4, S5, S6), recession (S1r, S2r, S3r, S4r, S5r, S6r), and bleeding upon probing (S1b, S2b, S3b, S4b, S5b, S6b). The data was collected per sexton, as in Figure 7 below.

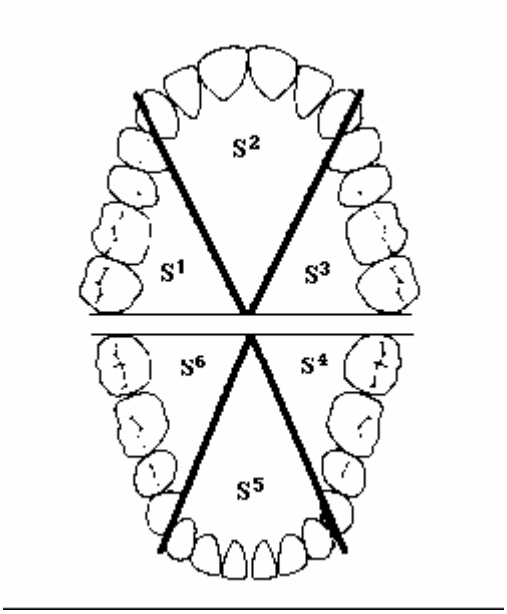

Figure 7 Sextant for PSR Exam

3.3.4.9 Malocclusion exam

This exam was used to explain the four dimensions of a participant's occlusion. The measurements included overjet, overbite, open bite, and displacement. An angles class was also determined for each participant.

3.3.4.10 Caries exam

A dentist or dental hygienist visually examined each surface of each tooth of the study participant. The dentist or dental hygienist performing the examination called out observations using codes provided in Figure 8, regarding reconstruction of tooth surfaces and other visual observations to the dental assistant who documented those observations.

COHRA Dental Examination

Age 1 to 6

COHRA

Barcode ID

4.8. Caries exam:

Coronal and root caries will be diagnosed using the following codes:

Surface Status	Code	Condition/Severity
Missing	01	Trauma
Missing	02	Ortho
Missing	03	Other
Missing	31	Other Decay
Missing	32	Other Perio
Missing	33	Other Unerupted
Missing	04	Pontic
Missing	41	Pontic Decay
Missing	42	Pontic Perio
Missing	43	Pontic Unerupted
Missing	05	Implants
Missing	51	Implants Decay
Missing	52	Implants Perio
Missing	53	Implants Unerupted
Healthy/Sound	06	Sound
Healthy/Sound	07	Sealed
Healthy/Sound	08	Stain
Healthy/Sound	09	Fluorosis
Healthy/Sound	10	Hypoplasia
Decay	11	White spot
Decay	12	Cavitation in enamel
Decay	13	Cavitation in dentin
Decay	14	Pulp exposure
Decay	15	Decay/recurrent
Restored	16	Restored
Root caries		Yes/No

Figure 8 Dental caries exam diagnosis code

3.3.4.11 Trauma exam

The dentist or dental hygienist visually assessed the teeth of the participant for any signs of oral trauma, such as fractures or complete loss of teeth.

3.3.4.12 Throat swab

A long swab was used to collect a sample from the participant's throat.

3.3.5 Station 5

At station 5, participants were interviewed by the research assistant or nurse regarding their oral health attitudes and behaviors using the Dental/Oral Health questionnaires.

3.3.6 Station 6

A trained nurse/medical examiner obtained a medical, family, and pregnancy (females only) history from the study participants at Station 6. A physical exam was also performed at this station.

3.4 STATISTICAL ANALYSIS

3.4.1 Participant demographics

The data used in these analyses were from the first visit only of each participant. The participants were seen at three clinic sites in Pennsylvania: Braddock (7.67%), Bradford

(13.00%), and Burgettstown (14.02%), and clinic sites in West Virginia (65.14%), totaling 2,570 study participants from 525 families. Of those individuals, 1,139 were males (44.32%) and 1,431 were females (55.68%). The majority of the patient population was Caucasian (80.31%). Individuals identifying themselves as African American (6.50%), Hispanic (0.82%), Asian (0.27%), Native American/Alaskan Native (0.16%), and "Other" (1.17%) also participated in the study. Some of the participants neglected to indicate a representative race (10.78%).

Information regarding relationship to other participants, sex and race were obtained using the initial intake form and screening interview form. Biological information was provided by the dental examination packet filled out by the dental hygienist and assistants throughout the appointment.

3.4.2 S.A.G.E.

The data collected in this study were organized into to a data set including a family ID, individual ID, sex, race, and the data listed in Tables 4 and 5. The FCOR program of the S.A.G.E. (Statistical Analysis for Genetic Epidemiology) package was used to identify any familial correlations within the data.

S.A.G.E. contains multiple C++ programs used in genetic analysis. The FCOR program was used to estimate a family correlation for pair types, such as parent-parent, parent-child, and sibling-sibling, for the variables of interest. FCOR uses the equation in Figure 9 below to calculate the correlation between the pairs.

$$r_{xy} = \frac{\sum_{i=1}^{N} w_i(x_i - \overline{x})(y_i - \overline{y})}{\sqrt{\sum_{i=1}^{N} w_i(x_i - \overline{x})^2 \sum_{i=1}^{N} w_i(y_i - \overline{y})^2}}$$

where $\overline{x} = \sum_i w_i x_i / \sum_i w_i$ and $\overline{y} = \sum_i w_i y_i / \sum_i w_i$ for arbitrary non-negative weights $\{w_i\}$.

Figure 9 Correlation equation [30]

S.A.G.E. used the data which was organized into pedigrees based upon assigned family ID and individual ID. FCOR analyzed pairs to determine correlations between family members regarding the traits in question. For FCOR to analyze a pedigree, at least two parents and a child of the same family ID were required. In some instances, only a parent and their child participated in the study. 817 individuals with a missing value for the trait of interest were created in the dataset in order to complete these families in the absence of an observed parent couple-child trio. 611 male (74.79%) and 140 female (17.14%) participants were created to form family trios. These created individuals were not included in the above demographic information.

Periodontal disease and dental caries can be highly influenced by the environment. In the data analyses, mother-father pair-types were to account for a base line correlation that would occur between non-related individuals due to their environment. Sibling-sibling pairs were used in the attempt to account for the many common environmental factors shared between family members. Parent:offspring pairs were to represent a genetic influence and limited shared environmental factors. Equal weight was given to each pair in the analysis. In the output, the program indentified the number of pairs used in the analysis, which is called the count. In some instances, an individual is used in more than one pair, such as a mother of three children. FCOR can account for those used more than once through its weighting scheme. FCOR provides the equivalence count, which is called the equiv count in the results section, reflecting the number of

independent pairs needed to obtain a similar standard error as that observed in the family data or the effective sample size. .

3.4.2.1 Aim 1: Determine if the ability to host supragingival bacteria (*S. mutans*) and subgingival bacteria (*Porphyromonas gingivalis*, *Treponema denticola*, and *Tannerella forsythensis* (formally known as *Bacteriodes forsythus*)) within the supragingival and subgingival plaque has a genetic and/or familial component

FCOR, a statistical program contained within S.A.G.E., was used to determine the presence of a family correlation in the ability to host bacteria within plaque. Data collected during the dental screening exam regarding subgingival (BANA™ test) and supragingival (Dentocult® test) were used in the analyses. No subgingival plaque from reference teeth were collected from children 6 years or younger, or from those children in which premedication was needed and therefore excluded from those sections of the analysis requiring those data.

Table 5 Data used in Aim 1 analyses and eligibility based upon age

	Age 1 – 6 years	**Age 7 – 10 years**	**Age 11 – 17 years**	**Age ≥ 18 years**
Supragingival plaque samples (Dentocult®)	YES	YES	YES	YES
Supragingival plaque sample from tongue (Dentocult®)	YES	YES	YES	YES
Subgingival plaque samples from reference teeth (BANA™)	NO	YES if no pre-med needed	YES if not pre-med needed	YES
Subgingival plaque sample from tongue (BANA™)	YES	YES	YES	YES

3.4.2.2 Aim 2: Investigate familiality in development of caries and periodontal disease

FCOR was also used for aim 2, which was investigating a family correlation in the development of dental caries and periodontal disease. Using the caries form (found in Appendix F), the DMFT and DMFS were calculated as indicators of dental caries development. Probing depth (measured using PSR) and bleeding on probing were used as periodontal disease indicators.

Some information was not available for analysis based upon the age of the study participant.

Table 6 Data used in Aim 2 analyses and eligibility based upon age

	Age 1 – 6 years	**Age 7 – 10 years**	**Age 11 – 17 years**	**Age ≥ 18 years**
Edentulous	YES	YES	YES	YES
Periodontal screening (PSR) for reference teeth	NO	YES if no pre-med needed	YES if no pre-med needed	YES
Recession from reference teeth	NO	YES	YES	YES
Bleeding upon probing from reference teeth	NO	YES	YES	YES
Periodontal screening (PSR) from sextons	NO	NO	NO	YES
Recession from sextons	NO	NO	NO	YES
Bleeding upon probing from sextons	NO	NO	NO	YES
Caries exam	YES	YES	YES	YES

3.4.2.3 Explanation of variables

The following is an explanation of the variables used throughout the data analysis.

Table 7 Explanation of variables used for AIM 1

Variable	Explanation
PlaqSam1	Plaque Sample taken from the surface of intact enamel
PlaqSam2	Plaque Sample taken from the surface of white spot lesion
PlaqSam3	Plaque Sample taken from the surface of cavitated initial enamel lesions
PlaqSam4	Plaque Sample taken from the excavated dentin from deep dentin lesions
PlaqSam5	Plaque Sample taken from a tongue scraping
TestR	Tongue scraping sample taken to use for the Dentocult® SM Strip mutans test
SupTestR#	Result of the Dentocult® SM Strip mutans test on the supragingival plaque sample taken
TungRes	Tongue scraping sample taken to use for the BANA-Zyme™ test
BANA#	Sample of subgingival plaque taken from tooth # for the BANA-Zyme™ test

Table 8 Explanation of variables used for AIM 2

Variable	Explanation
DMFS	decayed + filled + missing tooth surfaces
DMFT	decayed + filled + missing teeth
BL#	Identification of bleeding at the site of the BANA™ sample for tooth #
PSR#	Periodontal screening and recording at the site of the BANA™ sample for tooth #
REC#	Identification of recession at the site of the BANA™ sample for tooth #
S#	PSR value for sexton #
S#b	Identification of bleeding at sexton #
S#r	Identification of recession at sexton #

4.0 RESULTS

The tables provided in this section are compiled of output data from the statistical program FCOR as described above. FCOR is part of S.A.G.E., a statistical package used in the analysis of genetic and epidemiological studies. Only those correlations found to be statistically significant (different from zero with $p \leq 0.05$) in at least three pair-types were included in the tables. Three pair-types were used to be able to best interpret the influence of environmental influences as compared to genetic factors. Correlations with a standard error of > 10.0 were also not included in the tables due to the inability to interpret the meaning of such correlations. Tables including all correlations statistically different from zero are included in Appendix H. Table 9 and Table 10 indicate those results that were and were not statistically significant ($p \leq 0.05$) in three pair-types and those that were not.

Table 9 Statistically significant in three pair-types versus not in three pair-types for Aim 1

Aim 1	
Statistically Significant in three pair-types	**Not Statistically Significant in three pair-types**
Plaque Samples	
PlaqSam2:PlaqSam2	PlaqSam1:PlaqSam1
PlaqSam2:PlaqSam3	PlaqSam1:PlaqSam2
PlaqSam3:PlaqSam2	PlaqSam1:PlaqSam3
PlaqSam3:PlaqSam3	PlaqSam1:PlaqSam4
PlaqSam4:PlaqSam4	PlaqSam1:PlaqSam5
	PlaqSam2:PlaqSam1
	PlaqSam2:PlaqSam4
	PlaqSam2:PlaqSam5

Table 9 continued

	PlaqSam3:PlaqSam1
	PlaqSam3:PlaqSam4
	PlaqSam3:PlaqSam5
	PlaqSam4:PlaqSam1
	PlaqSam4:PlaqSam2
	PlaqSam4:PlaqSam3
	PlaqSam4:PlaqSam5
	PlaqSam5:PlaqSam1
	PlaqSam5:PlaqSam2
	PlaqSam5:PlaqSam3
	PlaqSam5:PlaqSam4
	PlaqSam5:PlaqSam5
Dentocult Results	
	TestR:TestR
	TestR:SupTestR
	TestR:SupTestR2
	TestR:SupTestR3
	SupTestR:TestR
	SupTestR:SupTestR
	SupTestR:SupTestR2
	SupTestR:SupTestR3
	SupTestR:SupTestR4
	SupTestR2:TestR
	SupTestR2:SupTestR
	SupTestR2:SupTestR2
	SupTestR2:SupTestR3
	SupTestR2:SupTestR4
	SupTestR3:TestR
	SupTestR3:SupTestR
	SupTestR3:SupTestR2
	SupTestR3:SupTestR3
	SupTestR3:SupTestR4
	SupTestR4:TestR
	SupTestR4:SupTestR
	SupTestR4:SupTestR2
	SupTestR4:SupTestR3
	SupTestR4:SupTestR4
BANA Results	

Table 9 continued

TungRes:TungRes	TungRes:Btest03
Btest14:Btest19	TungRes:Btest14
	TungRes:Btest19
	TungRes:Btest30
	Btest03:TungRes
	Btest03:Btest03
	Btest03:Btest14
	Btest03:Btest19
	Btest03:Btest30
	Btest14:TungRes
	Btest14:Btest03
	Btest14:Btest14
	Btest14:Btest30
	Btest19:TungRes
	Btest19:Btest03
	Btest19:Btest14
	Btest19:Btest19
	Btest19:Btest30
	Btest30:TungRes
	Btest30:Btest03
	Btest30:Btest14
	Btest30:Btest19
	Btest30:Btest30

Table 10 Statistically significant in three pair-types versus not in three pair-types for Aim 2

Aim 2	
Statistically Significant in three pair-types	**Not Statistically Significant in three pair-types**
DMFS and DMFT measurements	
permgenDMFS:permgenDMFS	permgeDMFS:permconseverDMFS
pergenDMFS:permgenDMFT	pergenDMFS:permconservDMFT
permgenDMFT:permgenDMFS	permgenDMFT:permconservDMFS
permgenDMFT:permgenDMFT	permgenDMFT:permconservDMFT
	permconservDMFS:permgenDMFS
	permconservDMFS:permgenDMFT
	permconservDMFS:permconservDMFS
	permconservDMFS:permconservDMFT
	permconservDMFT:permgenDMFS

Table 10 continued

	permconservDMFT:permgenDMFT
	permconserveDMFT:permconservDMFS
	permconservDMFT:permconservDMFT
Bleeding at BANA site	
Btest03:Btest03	
Btest03:Btest14	
Btest03:Btest19	
Btest03:Btest30	
Btest14:Btest03	
Btest14:Btest14	
Btest14:Btest19	
Btest14:Btest30	
Btest19:Btest03	
Btest19:Btest14	
Btest19:Btest19	
Btest19:Btest30	
Btest30:Btest03	
Btest30:Btest14	
Btest30:Btest19	
Btest30:Btest30	
PSR at BANA site	
Btest03:Btest03	
Btest03:Btest14	
Btest03:Btest19	
Btest03:Btest30	
Btest14:Btest03	
Btest14:Btest14	
Btest14:Btest19	
Btest14:Btest30	
Btest19:Btest03	
Btest19:Btest14	
Btest19:Btest19	
Btest19:Btest30	
Btest30:Btest03	
Btest30:Btest14	
Btest30:Btest19	
Btest30:Btest30	
Recession at BANA site	

Table 10 continued

Btest03:Btest03	
Btest03:Btest14	
Btest03:Btest19	
Btest03:Btest30	
Btest14:Btest03	
Btest14:Btest14	
Btest14:Btest19	
Btest14:Btest30	
Btest19:Btest03	
Btest19:Btest14	
Btest19:Btest19	
Btest19:Btest30	
Btest30:Btest03	
Btest30:Btest14	
Btest30:Btest19	
Btest30:Btest30	
Sexton Bleeding results	
	S1b:S1b
	S1b:S2b
	S1b:S3b
	S1b:S4b
	S1b:S5b
	S1b:S6b
	S2b:S1b
	S2b:S2b
	S2b:S3b
	S2b:S4b
	S2b:S5b
	S2b:S6b
	S3b:S1b
	S3b:S2b
	S3b:S3b
	S3b:S4b
	S3b:S5b
	S3b:S6b
	S4b:S1b
	S4b:S2b
	S4b:S3b

Table 10 continued

	S4b:S4b
	S4b:S5b
	S4b:S6b
	S5b:S1b
	S5b:S2b
	S5b:S3b
	S5b:S4b
	S5b:S5b
	S5b:S6b
	S6b:S1b
	S6b:S2b
	S6b:S3b
	S6b:S4b
	S6b:S5b
	S6b:S6b
Sexton PSR results	
	S1:S1
	S1:S2
	S1:S3
	S1:S4
	S1:S5
	S1:S6
	S2:S1
	S2:S2
	S2:S3
	S2:S4
	S2:S5
	S2:S6
	S3:S1
	S3:S2
	S3:S3
	S3:S4
	S3:S5
	S3:S6
	S4:S1
	S4:S2
	S4:S3
	S4:S4

Table 10 continued

	S4:S5
	S4:S6
	S5:S1
	S5:S2
	S5:S3
	S5:S4
	S5:S5
	S5:S6
	S6:S1
	S6:S2
	S6:S3
	S6:S4
	S6:S5
	S6:S6
Sexton Recession results	
	S1r:S1r
	S1r:S2r
	S1r:S3r
	S1r:S4r
	S1r:S5r
	S1r:S6r
	S2r:S1r
	S2r:S2r
	S2r:S3r
	S2r:S4r
	S2r:S5r
	S2r:S6r
	S3r:S1r
	S3r:S2r
	S3r:S3r
	S3r:S4r
	S3r:S5r
	S3r:S6r
	S4r:S1r
	S4r:S2r
	S4r:S3r
	S4r:S4r
	S4r:S5r

Table 10 continued

	S4r:S6r
	S5r:S1r
	S5r:S2r
	S5r:S3r
	S5r:S4r
	S5r:S5r
	S5r:S6r
	S6r:S1r
	S6r:S2r
	S6r:S3r
	S6r:S4r
	S6r:S5r
	S6r:S6r

Mother:father pair-types were used as a base line correlation value. They provide a correlation coefficient based upon no shared genetic information and limited shared environmental factors. Sibling:sibling and parent:offspring pair-types were also used to consider genetic influences. Parent:offspring and sibling:sibling pairs share 50% of their genetic make-up. However, siblings are more likely to share a greater amount of environmental influences than parent:offspring pairs. Half-sibling:half-sibling pair-types were also included in the data analysis as a means of evaluating environmental versus genetic influences.

Relational correlations and cross-correlations were produced throughout this analysis. The interpretation of the data output was the same for both types of correlations. However, the results of this study focus on those correlations obtained from the same trait in two individuals. The table present the results of the study as trait 1 of person 1:trait 1 of person 2. Count is the number of pairs that were used in the analysis while equiv. count reflects the effective sample size.

4.1 AIM 1: DETERMINE IF THE ABILITY TO HOST SUPREGINGIVAL BACTERIA (*S. MUTANS*) AND SUBGINGIVAL BACTERIA (*PORPHYROMONAS GINGIVALIS*, *TREPONEMA DENTICOLA*, AND *TANNERELLA FORSYTHENSIS* (FORMALLY KNOWN AS *BACTERIODES FORSYTHUS*)) WITHIN THE SUPRAGINGIVAL AND SUBGINGIVAL PLAQUE HAS A GENETIC AND/OR FAMILIAL COMPONENT

Data used for the analysis of Aim 1 were those that identified a microbial species.

Five potential plaque sample sites were identified. All individuals, unless they were edentulous, had plaque samples taken from the surface of intact enamel and the tongue scraping. If lesions were present, a sample was taken for evaluation.

Table 11 Significant correlation regarding plaque sample type across at least three pair-types

	PlaqSam2:PlaqSam2			PlaqSam2:PlaqSam3		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	370	369.6	0.37 ***	370	369.4	0.20 ***
Parent:Offspring	2054	1162.6	0.23 ***	2054	1290.1	0.07 *
Sibling	885	489.9	0.33 ***	885	811.2	0.12 ***
Half-Sibling						
	PlaqSam3:PlaqSam2			PlaqSam3:PlaqSam3		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	370	369	0.20 ***	370	369.4	0.24 ***
Parent:Offspring	2054	1225.8	0.11 ***	2054	1392.8	0.14 ***
Sibling	885	811.2	0.12 ***	885	585.4	0.20 ***
Half-Sibling						
	PlaqSam4:PlaqSam4					
	count	equiv count	correlation			
Mother:Father	370	369.3	0.24 ***			
Parent:Offspring	2054	1304.7	0.07 **			
Sibling	885	555.6	0.24 ***			
Half-Sibling	271	192.1	0.21 **			

*** $0.01 \leq p \leq 0.05$**

**** 0.001 ≤ p ≤ 0.009**
***** p ≤ 0.0009**
Standard error range for correlation values included in table: 0.0255 – 0.0691

As you can see in Table 11, plaque samples from lesions had correlations significantly different from zero in at least three pair-types. It is also observed that the correlations between mother:father and sibling:sibling are higher than that of parent:offspring. In addition, half-sibling:half-sibling correlations are very similar to those of full sibling pairs.

The Dentocult® SM Strip mutans test was used to identify the presence of *mutans streptococci* in the plaque samples taken from each participant. The possible test results are negative (0) and the presence allows for a spectrum (1, 2, and 3). The result for each sample was independent of the results of any other samples. The results from this analysis did not show a correlation statistically significant different from zero in the pair-types in question.

To explore the question of a familial correlation in the ability to host bacteria in subgingival plaque, the BANA-Zyme™ test was used. The possible results of the microbial test are negative (0), weak positive (1) or positive (2). The result for each BANA™ sample site was independent of the other site results.

Table 12 Significant correlation regarding BANA™ test result across at least three pair-types

	TungRes:TungRes			Btest14:Btest19		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	359	338.8	0.44 ***	344	312.9	0.12 *
Parent:Offspring	1855	954.8	0.34 ***	970	414.1	0.12 *
Sibling	776	392.7	0.39 ***	357	147.3	0.37 ***
Half-sibling	248	148	0.28 ***			

*** 0.01 ≤ p ≤ 0.05**
**** 0.001 ≤ p ≤ 0.009**
***** p ≤ 0.0009**
Standard error range for correlation values included in table: 0.0286 – 0.0759

As can be seen in Table 12, the bacteria results identified in the samples taken from the tongue in both individuals of the pair, and the bacteria taken from the 14th tooth of the first

individual and the 19th tooth of second individual were significantly correlated. The correlations of the tongue results are moderately correlated and similar across all pairs other than half-siblings, which is about half of the other pairs. The results from the tooth sites show a larger correlation coefficient between sibling pairs, with the correlation values of the other pairs being the same.

4.2 AIM 2: INVESTIGATE FAMILIALITY CORRELATION IN THE DEVELOPMENT OF CARIES AND PERIODONTAL DISEASE.

Data used for the analysis of Aim 2 were those that measured the development of dental caries and periodontal disease.

Data used to calculate the DMFS and DMFT were taken from the dental screening examination form, specifically the caries exam (found in Appendix F) and input into the equations found in Table 8.

Table 13 Significant correlation regarding DMFS and DMFT across at least three pair-types

	permgenDMFS:permgenDMFS			pergenDMFS:permgenDMFT		
pair-type	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	227	226.5	0.27 ***	228	227.4	0.23 ***
Parent:Offspring	795	370.8	0.25 ***	795	621.3	0.32 ***
Sibling	311	121.7	0.04 *	311	236.9	0.24 ***
Half-sibling						
	permgenDMFT:permgenDMFS			permgenDMFT:permgenDMFT		
pair-type	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	227	227.6	0.21 **	228	228.1	0.16 *
Parent:Offspring	795	355.9	0.23 ***	795	598.6	0.28 ***
Sibling	311	236.9	0.24 ***	311	263.8	0.36 ***
Half-sibling						

*** $0.01 \leq p \leq 0.05$**

**** 0.001 ≤ p ≤ 0.009**
***** p ≤ 0.0009**
Standard error range for correlation values included in table: 0.0362 – 0.0878

Table 13 shows some correlation in pair-types regarding caries indicators. Comparing DMFS:DMFS and DMFS:DMFT values, parent:offspring pairs show the highest degree of significant correlation. DMFT:DMFS appears to have correlations similar to one another and DMFT:DMFT indicating a moderately strong sibling correlation.

Indicators of periodontal disease, such as probing depth, bleeding upon probing, and recession, were used to investigate a familiality correlation in the development of periodontal disease. Probing depth, bleeding upon probing, and recession were examined for each BANA™ sample site and sexton.

Table 14 Significant correlation regarding bleeding at BANA™ sample sites across at least three pair-types

	BL03:BL03			BL03:BL14		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	370	369	0.15 **	370	370.1	0.16 **
Parent:Offspring	1082	776.3	0.15 ***	1082	767.3	0.15 ***
Sibling	387	262.8	0.24 ***	387	271.9	0.25 ***
Half-Sibling	93	74.7	0.26 *	93	77.9	0.25 *
	BL03:BL19			BL03:BL30		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	370	364.9	0.20 ***	370	368.5	0.17 ***
Parent:Offspring	1082	809.3	0.14 ***	1082	328.7	0.16 ***
Sibling	387	309.2	0.22 ***	387	319.9	0.20 ***
Half-Sibling				93	90.1	0.25 *
	BL14:BL03			BL14:BL14		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	370	367.8	0.18 ***	370	369.1	0.19 ***
Parent:Offspring	1082	760.1	0.16 ***	1082	751	0.16 ***
Sibling	387	271.9	0.25 ***	387	257.6	0.26 ***
Half-Sibling	93	77.9	0.25 *	93	73.8	0.25 *
	BL14:BL19			BL14:BL30		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	370	358.9	0.26 ***	370	364.5	0.23 ***

Table 14 continued

Parent:Offspring	1082	791.8	0.15 ***	1082	811.1	0.17 ***
Sibling	387	311.7	0.21 ***	387	322.7	0.19 ***
Half-Sibling				93	91.1	0.25 *
	BL19:BL03			BL19:BL14		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	370	371.9	0.15 **	370	375	0.16 **
Parent:Offspring	1082	748.5	0.16 ***	1082	739	0.17 ***
Sibling	387	309.2	0.22 ***	387	311.7	0.21 ***
Half-Sibling						
	BL19:BL19			BL19:BL30		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	370	369	0.22 ***	370	372.5	0.18 ***
Parent:Offspring	1082	782.9	0.18 ***	1082	802.8	0.20 ***
Sibling	387	275.4	0.21 ***	387	299.5	0.19 **
Half-Sibling						
	BL30:BL03			BL30:BL14		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	370	369.3	0.16 **	370	372.5	0.17 ***
Parent:Offspring	1082	758.9	0.18 ***	1082	749.4	0.18 ***
Sibling	387	319.9	0.20 ***	387	322.7	0.19 ***
Half-Sibling	93	90.1	0.25 *	93	91.1	0.25 *
	BL30:BL19			BL30:BL30		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	370	364.4	0.24 ***	370	368.9	0.20 ***
Parent:Offspring	1082	794.6	0.19 ***	1082	814.4	022 ***
Sibling	387	299.5	0.19 **	387	291.2	0.17 **
Half-Sibling				93	79.4	0.25 *

*** $0.01 \leq p \leq 0.05$**
**** $0.001 \leq p \leq 0.009$**
***** $p \leq 0.0009$**
Standard error range for correlation values included in table: 0.0342 – 0.0583
Standard error range for half-sibling:half-sibling pair-type: 0.0993 – 0.1100

Using bleeding at the BANA™ sample site as the trait, analyses show that all of the sample sites are significantly correlated with one another across at least three pair-types. Fourteen of the sixteen site comparisons show parent:offspring pairs as having a correlation less than that of the mother:father and sibling:sibling pair-types.

Table 15 Significant correlation regarding PSR at BANA™ sample site across at least three pair-types

	PSR03:PSR03			PSR03:PSR14		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	370	369	0.16 **	370	370.8	0.17 **
Parent:Offspring	1082	767.2	0.16 ***	1082	779.3	0.16 ***
Sibling	387	260.6	0.25 ***	387	268.4	0.24 ***
Half-Sibling	93	74.4	0.26 *	93	76.3	0.24 *
	PSR03:PSR19			PSR03:PSR30		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	370	364.2	0.23 ***	370	366.9	0.19 ***
Parent:Offspring	1082	794.7	0.16 ***	1082	809.9	0.15 ***
Sibling	387	2998.2	0.23 ***	387	305.5	0.22 ***
Half-Sibling	93	85	0.24 *	93	86.5	0.24 *
	PSR14:PSR03			PSR14:PSR14		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	370	367	0.20 ***	370	369.1	0.20 ***
Parent:Offspring	1082	749.4	0.16 ***	1082	761.1	0.16 ***
Sibling	387	268.4	0.24 ***	387	265.1	0.24 ***
Half-Sibling	93	76.3	0.24 *			
	PSR14:PSR19			PSR14:PSR30		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	370	363.5	0.24 ***	370	366.4	0.21 ***
Parent:Offspring	1082	774.8	0.16 ***	1082	789.7	0.14 ***
Sibling	387	305.5	0.23 ***	387	314.4	0.21 ***
Half-Sibling	93	86.7	0.22 *	93	88.7	0.22 *
	PSR19:PSR03			PSR19:PSR14		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	370	372.6	0.17 ***	370	373.2	0.18 ***
Parent:Offspring	1082	737.8	0.16 ***	1082	748.2	0.16 ***
Sibling	387	2998.2	0.23 ***	387	305.5	0.23 ***
Half-Sibling	93	85	0.24 *	93	86.7	0.22 *
	PSR19:PSR19			PSR19:PSR30		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	370	369.1	0.24 ***	370	371.1	0.21 ***
Parent:Offspring	1082	762.9	0.18 ***	1082	778.4	0.17 ***
Sibling	387	271.2	0.22 ***	387	288.2	0.20 ***
Half-Sibling						
	PSR30:PSR03			PSR30:PSR14		

Table 15 continued

	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	370	370.7	0.17 **	370	371.1	0.17 ***
Parent:Offspring	1082	753	0.17 ***	1082	763.6	0.17 ***
Sibling	387	305.5	0.22 ***	387	314.4	0.21 ***
Half-Sibling	93	86.5	0.24 *	93	88.7	0.22 *
	PSR30:PSR19			PSR30:PSR30		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	370	366.6	0.23 ***	370	368.9	0.20 ***
Parent:Offspring	1082	779.4	0.19 ***	1082	795	0.18 ***
Sibling	387	288.2	0.20 ***	387	280.4	0.19 **
Half-Sibling						

*** 0.01 ≤ p ≤ 0.05**
**** 0.001 ≤ p ≤ 0.009**
***** p ≤ 0.0009**
Standard error range for correlation values included in table: 0.0343 – 0.0581
Standard error range for half-sibling:half-sibling pair-type: 0.1019 – 0.1111

Probing depths at the BANA™ sample site were significantly correlated across all pair-types. Mother:father pair-types show the largest correlation coefficient value out of the three pair-types.

Table 16 Significant correlation regarding recession at BANA™ sample site across at least three pair-types

	REC03:REC03			REC03:REC14		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	370	369	0.16 **	370	370.9	0.17 **
Parent:Offspring	1082	753.4	0.16 ***	1082	766.5	0.19 ***
Sibling	387	250.7	0.28 ***	387	260.8	0.27 ***
Half-Sibling	93	72.5	0.26 *	93	75.2	0.26 *
	REC03:REC19			REC03:REC30		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	370	365.1	0.22 ***	370	368.4	0.18 ***
Parent:Offspring	1082	794.4	0.15 ***	1082	810.9	0.15 ***
Sibling	387	290.4	0.26 ***	387	300.4	0.24 ***
Half-Sibling				93	85.8	0.24 *
	REC14:REC03			REC14:REC14		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	370	366.8	0.20 ***	370	369.1	0.20 ***
Parent:Offspring	1082	736.8	0.16 ***	1082	749.9	0.17 ***
Sibling	387	260.8	0.27 ***	387	257.1	0.26 ***

Table 16 continued

Half-Sibling	93	75.2	0.26 *	93	73.7	0.26 *
	REC14:REC19			REC14:REC30		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	370	361	0.26 ***	370	365.6	0.22 ***
Parent:Offspring	1082	777	0.15 ***	1082	793.4	0.16 ***
Sibling	387	297.8	0.25 ***	387	309.5	0.23 ***
Half-Sibling				93	88.1	0.24 *
	REC19:REC03			REC19:REC14		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	370	372.1	0.17 ***	370	374.5	0.18 ***
Parent:Offspring	1082	722.6	0.16 ***	1082	735.3	0.18 ***
Sibling	387	290.4	0.26 ***	387	297.8	0.25 ***
Half-Sibling						
	REC19:REC19			REC19:REC30		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	370	369.1	0.23 ***	370	371.8	0.19 ***
Parent:Offspring	1082	764.4	0.17 ***	1082	780.7	0.18 ***
Sibling	387	267.1	0.23 ***	387	285	0.21 ***
Half-Sibling						
	REC30:REC03			REC30:REC14		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	370	369.5	0.17 ***	370	371.8	0.18 ***
Parent:Offspring	1082	740	0.17 ***	1082	753	0.19 ***
Sibling	387	300.4	0.24 ***	387	309.5	0.23 ***
Half-Sibling	93	85.8	0.24 *	93	88.1	0.24 *
	REC30:REC19			REC30:REC30		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	370	365.5	0.23 ***	370	368.9	0.19 ***
Parent:Offspring	1082	782.6	0.18 ***	1082	799.3	0.19 ***
Sibling	387	285	0.21 ***	387	278.7	0.20 ***
Half-Sibling						

*** $0.01 \leq p \leq 0.05$**
**** $0.001 \leq p \leq 0.009$**
***** $p \leq 0.0009$**
Standard error range for correlation values included in table: 0.0343 – 0.0583
Standard error range for half-sibling:half-sibling pair-type: 0.1013 – 0.1107

Recession was found to be least correlated between parent:offspring pairs as compared to mother:father and sibling:sibling. In many cases, the sibling:sibling pair-type showed the highest significant correlation and was similar to the value for half-sibling pairs.

No significant correlations were identified regarding the PSR, bleeding, and recession results for the sextons of the mouth across at least three pair-types. In the case of sibling:sibling and parent:offspring pair-types, there too few individuals who had data from this procedure. Even among the mother:father pair-types, no significant correlations were observed.

5.0 DISCUSSION

This is one of a small number of studies conducted to assess familial correlations for the ability to host specific bacteria in plaque and the development of dental caries and periodontal disease. The presence of certain oral bacteria has been associated with an increased risk of cardiovascular disease, suggesting that those at a higher risk to host these specific bacteria may be more likely to develop cardiovascular disease. If there is a familial correlation regarding the presence of these bacteria in the mouth, it may suggest a need to improve our standard of care for those individuals who are predisposed to dental caries, periodontal disease and hosting those bacteria associated with those diseases. The purpose of this study was to 1) identify a familial correlation in the ability to host such bacteria and 2) identify a familial correlation in the development of dental caries and periodontal disease. The third purpose of this study was dependent upon the results of the first two aims. The third purpose was to suggest a revision to our dental health standard of care in the presence of familiality of the trait in question.

In general, these study results suggest that the influences of both an individual's environment and genetic make-up are involved in a complex manner in the ability to host specific bacteria in plaque and develop the oral conditions in question. For all of the variables analyzed, the correlations of all the relative pair-types were relatively similar and may overlap when considering the standard of error. This may suggest an importance of both environmental

and genetic factors, the inability of the statistical test used to accurately evaluate the features in question, and/or the influence of factors that were not considered in this study.

5.1 DISCUSSION OF RESULTS REGARDING AIM 1: DETERMINE IF THE ABILITY TO HOST SUPRAGINGIVAL BACTERIA (*S. MUTANS*) AND SUBGINGIVAL BACTERIA (*PORPHYROMONAS GINGIVALIS*, *TREPONEMA DENTICOLA*, AND *TANNERELLA FORSYTHENSIS* (FORMALLY KNOWN AS *BACTERIODES FORSYTHUS*)) WITHIN ORAL PLAQUE HAS A GENETIC AND/OR FAMILIAL COMPONENT

5.1.1 Supragingival plaque

Two different factors were investigated in this subsection of aim 1) presence of disease, and 2) presence of bacteria. The results of these different situations may have different implications.

The presence of disease appears to be under stronger environmental influence as compared to a genetic influence. This is supported in that mother:father pairs had larger correlation values when compared to parent:offspring. In addition, mother:father pairs had higher correlations than sibling:sibling pairs with the exception of samples taken from deep dentin lesion compared with itself and compared with tongue scraping. Since it is assumed that mother:father pairs share no genetic information, this is even greater support of environmental factors influencing the development of dental lesions, which many times lead to dental caries. In many cases, the correlation values of full sibling pairs and half-sibling pairs were very similar,

evidence that the dental traits may be explained by a small genetic component. Comparisons mentioned here were restricted to correlations which reached statistical significance. The implications of this are discussed further below.

The presence of *S. mutans* in supragingival plaque did not result in any correlations significantly different from zero across at least three relative pair-types. Many of the pair-type correlations used only a small number of pairs for analysis. This may have resulted in an inaccurate correlation. In addition, the small number of pairs that were available for analysis resulted in standard errors greater than or equal to 10.0. Given the variability in the correlation value due to the standard error, it was inappropriate to include these statistically significant correlations in the analysis compared with other pair-types. It is possible that these results suggest that the presence of *mutans streptococci* is uncorrelated among those with shared genetic information and those who share an environment. However, these results are unreliable given the small number of pairs included in the analysis.

5.1.2 Subgingival plaque

The BANA™ test identifies the presences of three anaerobic bacteria, *Porphyromonas gingivalis*, *Treponema denticola*, and *Tannerella forsythensis* (formally known as *Bacteriodes forsythus*) [31]. Many of the results pertaining to bacteria identified in the BANA™ test were not significantly correlated across at least three pair-types. Plaque collected from the tongue of both individuals in the pair showed similar correlations for all pair-types. Given these results, it is unclear that there is a genetic component to this feature. Plaque collected from tooth 14 and 19 showed higher correlation for the sibling:sibling pair-type. This may be evidence of the trait being influenced by genetic make-up. However, this cannot be said for certain since siblings

also share environmental factors. It is possible that environmental and genetic factors play a role in the presence of subgingival bacteria since the sibling pair correlation is greater than mother:father pair-type, which should be greater if environmental factors were the only crucial component.

5.1.2.1 Confounding factors and limitations specific to determining a familial correlation in the ability to host specific bacteria in subgingival plaque

The age of the participants determined the type of samples that could be taken. Children under the age of 6 years old did not participate in the subgingival plaque collection for the BANA™ test. Therefore, these results may not be applicable to young children and their parents in regards to the ability to host subgingival plaque.

The BANA™ test does not differentiate between *P. gingivalis*, *B. forsythus*, and *Treponema denticola* [31]. This study looked only at the degree in which bacteria was present in the mouth. It does not account for additional subgingival bacteria that may be in the mouth. The test also does not differentiate relative amounts of the different types of bacteria, which may influence the risk to develop cardiovascular disease.

5.2 DISCUSSION OF RESULTS REGARDING AIM 2: INVESTIGATE FAMILIALITY IN THE DEVELOPMENT OF CARIES AND PERIODONTAL DISEASE

5.2.1 Dental caries

DMFS and DMFT values have been used as a method to indicate and quantify the extent of dental caries. As indicated in Table 8, DMFS considers the tooth surfaces and quantifies the number decayed, missing and filled. DMFT considers the whole tooth and quantifies the number decayed, missing and filled. These values were then used to calculate the correlation.

Two different equations were used for DMFS and DMFT. A conservative value was calculated, which was stricter and more exclusive regarding the definition of decayed, missing and filled. The nonconservative value had a broader and more inclusive definition of decayed, missing, and filled. None of the conservative correlations were found to be statistically significant across three or more pair-types.

Primary and permanent teeth were also evaluated. Many of the adults in the study were not given a primary DMFS or DMFT due to not having primary teeth remaining in the mouth. Therefore, DMFS and DMFT values for permanent teeth only were used in the analysis.

DMFS values of parents compared to their offspring showed a larger correlation coefficient than among the parent pairs and sibling pairs. This is evidence that genetic factors may influence decay, loss, or need to fill teeth. Given that parents and their children are still likely to share some of the environmental influences, the impact of the environment cannot be ruled out.

Parent DMFT values compared with their offspring did not show the same result and was found to have values in between the other groups. Sibling pair DMFT values showed the highest significant correlation. However, given the range of the standard error, these values are likely to overlap, complicating the interpretation of the results.

5.2.1.1 Confounding factors and limitations specific to investigating the familiality of the development of dental caries

There is evidence that the development of dental caries has many stages of disease [10]. These include white spot lesions, cavitated enamel, and repaired dentin. White spots are not always observable and may only be detected with the use of an x-ray [10]. In the study, only a visual caries exam was performed, therefore, it is possible that some early signs of dental caries may have not been identified.

Tooth structure and shape has been shown to influence the ability to remove plaque on the tooth surface [10]. These features were not considered in the data that was collected for each participant. Therefore, it is possible that these features may have confounded the results.

DMFT and DMFS calculation do not consider early event evidence of dental decay, such as the white spot [5]. DMF does not include the variability of expression of these conditions [10]. DMFS may also be subject to over-treatment effects. Unnecessary fillings may have been performed as a preventative or over-cautious measurement. During the dental screening examination, necessary and unnecessary dental caries fillings were indistinguishable.

5.2.2 Periodontal disease

Probing depth (PSR), bleeding upon probing, and recession have been identified as predictors of periodontal disease and were used in this study as such. These measurements were evaluated for each site in which a sample was taken for the BANA™ test as well as the value for each sexton of the mouth.

The results from the sites in which a sample for the BANA™ test were taken showed a significant correlation across at least three pair-types for each site comparison. The results of the sexton measurements did not show significant correlation across at least three pair-types in any of the comparisons. This was likely due to the small number of pairs available for results as well as the lack of significant correlations between parent:offspring pair-types. Therefore, only the results from the BANA™ comparisons will be used.

All of the site comparisons, with the exception of two sites measures for bleeding upon probing, resulted in the parent:offspring pair-type having the lowest correlation coefficient value. The correlation coefficients in the majority of comparisons were similar and may overlap when considering the standard error. In addition, many cases in which the half-sibling:half-sibling pairs show a significant correlation coefficient, the value was similar to that of the sibling:sibling pair-types.

5.2.2.1 Confounding factors and limitations specific to the investigation of the familiality of the development of periodontal disease

Participants under the age of 6 did not have any sample taken for BANA™ or measurements for PSR, bleeding upon probing or recession. Those participants between the ages of 7 and 17 years old did not have sexton measurements taken but fully participated in the

BANA™ procedure, including PSR, bleeding upon probing, and recession measurements. This may influence the lack of data for the sextons and be the cause of the low number of pairs. Also, this limits the detection of the beginning stages of periodontal disease which may be evident under 6 years of age.

Cigarette smoking has been shown to be as important as microbiological factors in determining periodontal severity [14]. Environmental factors, such as smoking, were not accounted for in the analysis of the data. It is possible that correlations may change when these factors are considered.

Periodontal disease has a variable expression. Measuring the presence or severity by deep pockets does not encompass the variability in the disease expressivity [10]. Bleeding upon probing and recession were also considered as features of periodontitis in this study. There are other characteristics of periodontal disease they may not have been identified.

5.3 DISCUSSION OF CONFOUNDING FACTORS AND LIMITATIONS

In the process of this study, many confounding factors and limitations became apparent. Most importantly, oral hygiene of each study participant was not taken in to account. Many studies have shown that brushing and flossing can reduce the amount of plaque detected on the surface of the tooth, as well as those bacteria near the gum line [8]. The addition of mouth wash can further reduce the amount of bacteria in the mouth. The oral hygiene status of the participant may be an important factor in determining disease risk. Pair-types were used as a method to tease out environmental factors (mother:father and sibling:sibling) versus genetic factors (parent:offspring) that play a role in hosting bacteria and oral disease. Information on the oral

health habits of each participant may be important since a mother and father may not have similar health habits. This would allow for one important variable to be controlled.

Specific environmental factors may play a role in disease development, such as socioeconomic status and access to health care. These factors may limit the access to oral health educational services and material, as well as dental care that has been shown to be beneficial in the reduction of plaque and maintenance of oral health. Certain types of medication and cigarette smoking have been shown to influence the development of dental disease [14]. Cigarette smoking has been shown to be as important as microbiological factors in periodontal severity. Diet and stress also play a role in the amount and type of bacteria found in the mouth as well as dental cavities and periodontal disease. Data regarding these potential factors were collected through the study but were not considered in the data analysis.

The definition regarding environment between individuals was restrictive and perhaps outdated. Generational proximity was the prominent characteristic in determining amount of shared environment between pairs. During this study, it was assumed that siblings shared the greatest amount of environmental factors and parents shared the least. The individual's age, relationship and interaction with different family members, and living situation may influence the amount of environmental factors shared between pair-types. Accounting for these uncertainties is complicated by the unique relationship and interaction of each family and the members of that family. In addition, shared individual-level environmental factors also need to be considered. Such shared factors may include the number of bathrooms in the home, affecting the amount of shared time and exposures in that area, as well as dietary habits, which influence the types of food to which an individual may be exposed,

The age of the participant was a large confounding factor in this study. Age determined the type of samples that could be obtained and procedures that could be performed. This may have influenced the results of the data due to samples or measurements that could not be collected. It is possible also that some of the data analyzed may have different results for the same individual dependent upon their age. Periodontal disease is seen more commonly in individuals over the age of 65 [13] but it unclear as to if it is due solely to environmental influences or if their genetic make-up played a role as well. Siblings are also more likely to share many environmental factors with one another if they are of similar age. The large amount of shared environmental factors may create noise in the data and complicate interpretation. There may be so many similar environmental factors that they negate the role of genetic make-up that may be detected. Age also may affect the opportunity for more shared environmental factors. Parent couples have most likely spent more time in a shared environment than sibling pairs. Sibling pairs have a shared environment for only as long as the age of the youngest child. Therefore, it is possible that parent pairs have spent more time in a similar environment and that the oldest child has shared more environmental factors with their parents than their youngest sibling.

An additional factor that was noted through the analysis of the COHRA data was that more females were involved in the study than males. The demographics of this population appeared to be fairly balanced between males and females; however, many of the males in the study were children of female participants. Due to this bias, more data was collected on females and their children as compared to males and their children.

It is possible that the results may be biased due to the inclusionary criteria for the data analysis. Only those correlations that were statistically significant were included in the analysis. Due to this criterion, it is important to cautiously interpret the current study's findings because

correlations encompassing zero through lack of statistical significance were not included for consideration here. A correlation of zero or non-significant correlation would indicate that there is no evidence of a non-zero correlation and would be an important result.

5.4 CONCLUSION

The results of this study suggest that environmental factors play a role in the ability to host supragingival and subgingival bacteria, as well the development of dental caries and periodontal disease. The degrees to which genetic factors are involved is still unclear based on the results of this study alone. This has made the need for additional studies more apparent.

5.4.1 Aim 3: If the family correlations are consistent with a significant genetic component, investigate possible modifications to current dental health recommendations

The results of this study do not support the need to adjust the current oral health standard of care at this time. The influences of the environment and an individual's genetic make-up appear to be complex. More evidence and understanding through clinical and scientific studies are necessary if changes are to be recommended.

5.4.2 Implication for public health and clinical care

The link between cardiovascular disease and oral health continues to be supported through clinical studies and research. As the knowledge regarding the relationship between the diseases become more defined, efforts will be put forth to determine how to lower the risk of cardiovascular disease through oral health. If the role of environment and genetic factors can be clarified, individuals at risk for these diseases may be identified and preventative and risk reduction interventions can be applied.

Further investigation into the influences of dental caries and periodontal disease is necessary to determine how to best treat patients. The need is no longer simply for good oral health, but overall health, especially cardiovascular. As the relationships and influences of these conditions become clearer, clinical care can adapt to incorporate the new information and treat patients in the best way possible.

5.4.3 Implications for future studies

More studies are necessary to further define the association between cardiovascular disease and oral health. Knowing the relationship between these conditions will allow us to determine if dental caries and periodontal disease may be a marker for risk or a causal factor [16]. Should these oral health conditions be found to be as causal factors, their prevention and management may lead to a decrease in the development of other serious systemic diseases, such as cardiovascular disease [5].

Humphrey et al. suggested that longitudinal studies beginning in childhood and randomized controlled trials (acknowledging the ethical issues) be conducted. In any study that

is carried out, standardized definitions and measurements of dental caries, periodontal disease, and cardiovascular disease will need to be determined and should include careful and consistent follow-up [16].

The identification of genetic risk factors (via linkage) in combination with environmental factors and microbial make up may allow for at-risk individuals to be identified, pre-symptomatic treatment, or avoidance of certain behaviors (i.e. smoking) [14].

Studies accounting for confounding factors and limitations in this study should be performed. An understanding of factors such as age, cigarette smoking, and oral hygiene behaviors, may provide clarification of the different roles that genetic and environmental factors play in oral health.

The results from this study should be reinterpreted with all those values without a significant p-value. Important information may have been lost due to the inclusionary criteria for the data analysis.

Further studies in the relationship between oral health, environmental factors and genetic make-up are necessary to determine the best plan of treatment. This knowledge may be able to assist in offering prophylactic care to children who are at high risk of developing dental caries or periodontal disease. Reducing the incidence of oral health disease may help to reduce the incidence of cardiovascular disease and other health concerns.

APPENDIX A

STUDY PARTICIPANT CONSENT FORM FOR PENNSYLVANIA SITES

CONSENT TO BE A SUBJECT IN A RESEARCH STUDY

TITLE: **Genetic Factors Contributing to Oral Health Disparities in Appalachia (Pennsylvania Sites)**

PRINCIPAL INVESTIGATOR: Mary L. Marazita, Ph.D., F.A.C.M.G.
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CO-INVESTIGATORS: Robert J. Weyant, D.M.D., Ph.D.
Head, Division of Pediatric and Developmental Dental Sciences
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Louise Platt-Schulhof, RDH, MHPE, CHES
UPMC Braddock
400 Holland Avenue
Braddock, PA 15104

Telephone: 412-636-5276

SOURCE OF SUPPORT: National Institute of Dental and Craniofacial Research, U.S.A.

Why is this research being done?

Dr. Marazita and Dr. Weyant invite you to be in a study to learn more about dental health in families, including behaviors, genes (those factors that determine a person's physical characteristics and have been passed to them from their parents), and periodontal (gum tissue) factors. Oral health varies greatly among different people. The purpose of this study is to identify which genes, attitudes, and behaviors play a role in people's oral health, so that risk factors for oral health problems can be better understood.

Who is being asked to take part in this research study?

You are a member of one of approximately 700 families from West Virginia or Western Pennsylvania with at least one child between 1 and 18 years old, who is being asked to participate in this study. Your family is part of a representative sample of similar families in Braddock, Pennsylvania.

What procedures are being performed for research purposes?

You and your family will be asked to participate in a 4-part examination process during this visit. You and your family will also be asked to return every two years, for a total of three or four visits over five to seven years. If you agree to participate, you will undergo the following procedures during this visit. You have the right to participate in only one, two, three, or all four parts of the examination:

Part 1) Questionnaires: You will be asked a series of questions about your behaviors, thoughts, and opinions regarding dental health, general health, prevention, family relationships, parenting practices, social relationships, alcohol, drug and tobacco use, and mental health (for example, self esteem and mental illness). Demographic information (for example, age) and general health history (for example, vaccinations and frequency of check ups) also will be recorded. In addition, you will be asked to complete questionnaires that focus on medical symptoms, dental anxiety, and social history. You will be given an opportunity to examine these questionnaires and do not have to answer all the questions. This part of the study will take about 2 hours.

Part 2) Dental, Microbiological and Tobacco Examinations: You will be given a dental screening to document the presence of oral conditions, including dental decay (cavities), gum infections (called gingivitis and periodontitis by dentists), tooth alignment and crowding, dental or oral injury, and a variety of other conditions of the teeth and mouth (for example, thin enamel). The dental exam will be conducted by a licensed dentist or dental hygienist and is similar to a routine checkup visit to a family dentist, except no x-rays will be taken. During this exam, you will be asked questions regarding your dental status, such as history of tooth injury, and brushing and flossing habits. All people have different kinds of bacteria present in their mouth, so the purpose of the oral microbiological exam is to test your saliva ("spit") and the plaque on your teeth for bacteria that could cause cavities or gum infections. For this examination, you will provide a saliva sample by chewing on a wax pellet and then spitting into

a vial. You will have a test to check the flow of your saliva. Your saliva will also be used to check if there is any evidence of tobacco use. A plastic strip will be placed on your tongue to collect saliva. The inside of your cheek may also be scraped to collect a sample. Dental instruments and special toothpicks will be used to scrape and collect dental plaque from your teeth and tongue. A long Q-tip will be used to collect a throat swab from the back of your throat. If any dental problems are found, you will be given referral information and can seek dental care at your own expense. Dental care will not be provided as part of this study. This part of the study will take about 1 hour.

Part 3) Blood sample for DNA studies: Approximately one and one half teaspoons blood will be used to evaluate your DNA for genes relating to dental health, such as those which affect cavities, tooth development, or wound healing. If you are unwilling to give a blood sample, you will be provided some mouthwash and the rinse will be collected, or the inside of your cheek will be swabbed with several brushes to collect cells that contain DNA. If you are unwilling to give a blood sample, you have the option of providing a saliva (spit) sample or having the inside of your cheek swabbed with several cotton swabs to collect cells that contain DNA. If necessary, you could also be provided some mouthwash to rinse to collect the DNA. This part of the study will take 5 minutes or less, and will only be done at one visit, unless the sample is insufficient to complete the study.

Part 4) Water Sampling: You have been sent a vial to collect a sample of your drinking water from your home. This water will be tested for fluoride, a mineral in some people's water that can prevent cavities. Please bring this vial with you to your appointment.

What are the possible risks, side effects, and discomforts of participating in this research study?

1) The questions in the interviews and questionnaires may be personal. If any information about child abuse, neglect, or mistreatment is uncovered, then the law requires that it be reported.
2) The dental screening infrequently causes some slight gum bleeding, which usually stops within a few minutes. If you have a serious gum infection, you may be sensitive to the gum examination. There is a rare risk that probing your gums may cause an abscess, or infection, of the gum tissue. Although this is rare and usually goes away within a short period of time, it might be painful and require treatment with antibiotics.
3) The gum examination is usually not a risky procedure for most healthy people. But, if you have had previous bacterial (infective) endocarditis, certain specific and serious congenital (present from birth) heart conditions, or artificial heart valves or have had a knee or hip replaced, this examination could place you at risk for a bacterial infection that would affect your heart and the joints in your bones. You will be asked if you have ever had any of these heart or joint problems, and if so, you will be asked to obtain and take an antibiotic (either amoxicillin or clindamycin, azithromycin, or clarithromycin) at your own expense an hour before the gum examination.
If you have the reduced ability to resist infection, this examination could place you at risk for developing an infection. If you have the reduced ability to form blood clots, you could be at risk for mild, but prolonged bleeding during some of the exam procedures. Prior to the dental exam, you will be asked in detail about having either of these conditions. If you have a reduced ability to resist infection or form blood clots, you will be excused from all parts of the examination that might cause bleeding.

4) Collection of tooth plaque, as well as the tongue and cheek scrapings, is likely to be briefly uncomfortable. The throat swab will likely lead to a brief gagging response.
5) The needle puncture of your vein to obtain the blood sample may infrequently result in pain and soreness, bruising, fainting, and rarely infection. This procedure will be performed by individuals trained and experienced in obtaining blood samples so as to minimize these risks.
6) In the unlikely event of a breach of confidentiality, there is a very remote possibility that the genetic information could affect your ability to be insured, employed, or your family relationships. Such problems are probably rare. You can ask the investigators about the likelihood of the research discovering anything that would lead to these problems.

What are the possible benefits of participating in this research study?

By participating, you may learn more about your own dental and overall health. You will receive verbal and written feedback about your dental screening. If your dental screening any significant problems, you will also receive names of some dentists or other health professionals who could help with any related dental/medical needs. The information obtained from your participation in this research study may eventually lead to a better understanding and better treatments for oral health problems.

If I agree to take part in this research study, will I be told of any new risks that may be found during the course of this study?

You will be promptly notified if any new information develops during the conduct of this research study, which may cause you to change your mind about continuing to participate.

Will I or my insurance company be charged for the cost of any procedures performed as part of this research study?

None of the services and/or procedures (Dental Screening, blood draws, etc.) you receive during this research study will be billed to you or your health insurance. If you get a bill or believe your health insurance has been billed for something that is part of the study, notify a member of the research team or UPMC Patient Billing Services.

You and your health insurance will be charged, in the standard manner, for services and procedures provided for your routine care. If you are required to take the prophylactic oral antibiotic prior to a dental exam, either you or your insurance company will be charged the cost of obtaining the antibiotic. The study will reimburse you for any out-of-pocket costs for the prophylactic antibiotic.

Will I be paid if I take part in this research study?

You will be paid $5.00 for each procedure of the study that you complete, with an added $5.00 if all four procedures are completed, up to $25.00 for one visit. Payment will be in the form of a gift card to your choice of Giant Eagle, Target, or Wal-Mart. Each time you return for the study (every 2 years for a total of 3 or 4 visits), you will be paid these same amounts. Over a 5 – 7 year period, you could potentially receive $75 - $100 dollars worth of gift cards depending on the total number of visits. You will also be reimbursed for any out-of-pocket expenses, including long distance communication, transportation, parking, one meal, and any costs of obtaining a blood sample at a local lab.

Who will pay if I am injured as a result of taking part in this study?

University of Pittsburgh researchers recognize the importance of your voluntary participation in their research studies. These individuals and their staffs will make reasonable efforts to minimize, control, and treat any injuries that may arise as a result of this research. If you believe that you are injured as a result of the research procedures being performed, please contact immediately the Principal Investigator listed on the first page of this form.
Emergency medical treatment of injuries solely and directly related to your participation in this research study will be provided to you by the hospitals of UPMC. It is possible that UPMC may bill your insurance provider for the costs of this emergency treatment, but none of these costs will be charged directly to you. If your research-related injury requires medical care beyond this emergency, you will be responsible for the costs of this follow-up care unless otherwise specifically stated. There is no plan for monetary compensation. You do not, however, waive any legal rights by signing this form.

Who will know about my participation in this research study?

Any information obtained about you from this research study will be kept as confidential as possible. All information about you or your involvement in this research study will only be accessible to the investigators involved in this study and their research staff, and will not be released to anyone without your written permission. Records and information pertaining to your identity and involvement in this research study will be stored in locked file cabinets at the [School of Dentistry of the University of Pittsburgh or at UPMC Braddock. Computer records will be kept in password protected, secured databases. Your identity on data records, donated blood and dental samples, and DNA will be indicated only by code number. Records linking the codes to your personal identifying information will be stored in a separate, secure location. You will not be identified by name in any publication of the research results unless you sign a separate form giving your permission.

Will this research study involve the use or disclosure of my identifiable medical information?

This research study will NOT involve the use or disclosure of your identifiable medical information from your hospital or physician records, or future medical information that might become available during your participation in this study. This study will record some of your personal health or medical information, which will be kept separate from your medical records, and used only for research purposes.

Who will have access to identifiable information related to my participation in this research study?

The information learned about you during this study will not be released to anyone (for example, relatives, personal physicians, insurance companies, or any other third party) without your prior written permission. However, in the unlikely event that an interviewer identifies someone who is considered to be at immediate risk for harming him or herself or others, they will need to inform the appropriate agencies, as required by Pennsylvania law. Any information about child abuse, neglect, or mistreatment must also be reported. These research records, just like hospital records, may be subpoenaed by court order or may be inspected by federal regulatory authorities.

In addition to the investigators listed on the first page of this consent form and their research staff, the following individuals may have access to identifiable information related to your participation in this research study. Authorized representatives of the University of Pittsburgh Research Conduct and Compliance Office may review your identifiable research information for the purpose of monitoring the appropriate conduct of this research study. In addition, authorized representatives of the University of Pittsburgh may have access to this information for the purpose of making participant payments.

For how long will the investigators be permitted to use identifiable information related to my participation in this research study?

The investigators may continue to use identifiable information related to your participation in this research study for at least 5 years following the completion of the research study.

May I have access to my personal research information resulting from my participation in this research study?

You will be notified if you have any dental problems. You will not be provided with your personal research or genetic information obtained during this study.

Is my participation in this study voluntary?

Your participation in this research study is completely voluntary. Whether or not you provide your consent for participation in this research study will have no effect on your current or future medical care at a UPMC Hospital or affiliated health care provider, or your current or future relationship with a health care insurance provider or with the University of Pittsburgh. If you turn 18 during the course of the study, your parent's permission is no longer valid, and you will be re-contacted to give permission as an adult.

May I withdraw, at a future date, my consent for participation in this research study?

You do not have to take part in this study and, should you change your mind, you can withdraw from the study at any time by submitting a dated, written request to withdraw to Dr. Marazita, who is listed on page 1 of this form. Any research information recorded before your withdrawal may continue to be used in the research study. Your decision to withdraw from this research study will have no effect on your current or future medical care at a UPMC Hospital or affiliated health care provider, or your current or future relationship with a health care insurance provider or with the University of Pittsburgh. You may be removed from the study by the investigators, if the information you provide is incorrect. If you withdraw or are removed from this research study, your biological samples, blood sample, and DNA will be destroyed.

Will my DNA samples be used for future studies?

Dr. Marazita will control the use of your biological samples and genetic material for this study, and will store your biological samples with codes in freezers at the University of Pittsburgh and West Virginia University. In the future, new research may identify other factors that could be involved in oral health. If this happens, Dr. Marazita would also like to examine them. Thus, if you agree, your biological samples and DNA will be saved for future testing of newly identified factors involved in oral health. When all of her research studies of oral health are completed, any remaining biological samples and DNA will be destroyed at that time. If you do NOT agree,

your biological samples and DNA will be discarded at the end of this particular research study. You may also be contacted in the future to be invited to participate in additional research, but that future involvement is voluntary as well. If you turn 18 during the course of the study, your parent's permission is no longer valid, and you will be re-contacted to give permission as an adult regarding the use of your DNA samples.

Your blood sample and its DNA used in this research study may contribute to a new invention or discovery. Sometimes, these inventions or discoveries may be of commercial value and may be sold, patented, or licensed by the investigators and the University of Pittsburgh for use in other research or the development of new products related to oral health**.** If the research investigators are able to develop new products from the use of your biological sample or genetic material, they currently have no plans to share any money or other rewards with you. You retain the right to have your blood sample and its DNA destroyed if you decide to withdraw from this research study.

****
****
******

I give my permission for Dr. Marazita to save my biological samples and genetic material, with personal identifiers, for use in other genetic research projects involving the study of oral health.

YES _____ NO _____

I give my permission to be re-contacted to obtain my consent if there is a desire to use my biological sample or genetic material, with personal identifiers, in other research projects involving the study of different diseases or conditions.

YES _____ NO _____

VOLUNTARY CONSENT AND AUTHORIZATION

All of the above has been explained to me and all of my current questions have been answered. I understand that I am encouraged to ask additional questions at any time about this research study, and that such future questions will be answered by the researchers listed on the first page of this form. Any questions I have about my rights as a research participant will be answered by the Human Subject Protection Advocate of the IRB Office, University of Pittsburgh (1-866-212-2668).

By signing this form, I agree to participate in this research study. A copy of this consent form will be given to me.

Adults aged 18 and over:

_____ _____

Participant's Signature Date

Children aged 1 – 17:

I understand that, as a minor (age less than 18 years),
_____ is not permitted to participate in this research study without my consent. Therefore, by signing this form, I give my consent for their participation in this research study.

_____ _____

Parent's Name Relationship to Participant (Child)

_____ _____

Parent's Signature Date

Children who can sign their name:

This research has been explained to me, and I agree to participate.

_____

Child's Name

_____ _____

Child's Signature Date

Verification of explanation for children who can sign their name:

I certify that I have carefully explained the nature and purpose of this research study to the above-named child in age-appropriate language. They have had an opportunity to discuss it with me in detail. I have answered all their questions, and they have provided assent to participate in this study.

_____ _____

Printed Name of Person Obtaining Consent Role in Research Study

_____ _____

Signature of Person Obtaining Consent Date

All participants:

CERTIFICATION OF INFORMED CONSENT

I certify that the nature and purpose of this research study have been explained to the above-named individual(s), and the potential benefits and possible risks of study participation have been discussed. Any questions the individual(s) have about this study have been answered, and we will always be available to address future questions as they arise. I further certify that no research component of this protocol was begun until after this consent form was signed.

_____

Investigator's Printed Name

_____ _____

Investigator's Signature Date

APPENDIX B

INSTITUTIONAL REVIEW BOARD APPROVAL LETTER FOR PENNSYLVANIA SITES

Resick, Judith Morya

From: irb+@pitt.edu
Sent: Tuesday, August 26, 2008 3:39 PM
To: Resick, Judith Morya
Subject: PI Notification: Your research study has been approved

University of Pittsburgh
Institutional Review Board

3500 Fifth Avenue
Pittsburgh, PA 15213
(412) 383-1480
(412) 383-1508 (fax)
http://www.irb.pitt.edu

Memorandum

To: DR. MARY MARAZITA

From: SUE BEERS PhD, Vice Chair

Date: 8/26/2008

IRB#: IRB020773

Subject: Genetic Factors Contributing to Oral Health Disparities in Appalachia.

Your research study has received expedited review and approval from the University of Pittsburgh Institutional Review Board under: 45 CFR 46 110.(9)

Please note the following information:

The advertisement that was submitted for review has been approved as written.

Approval Date: 8/25/2008
Expiration Date: 8/24/2009

Please note that it is the investigator's responsibility to report to the IRB any unanticipated problems involving risks to subjects or others [see 45 CFR 46.103(b)(5) and 21 CFR 56.108(b)]. The IRB Reference Manual (Chapter 3, Section 3.3) describes the reporting requirements for unanticipated problems which include, but are not limited to, adverse events. If you have any questions about this process, please contact the Adverse Events Coordinator at 412-383-1480.

The protocol and consent forms, along with a brief progress report must be resubmitted at least one month prior to the renewal date noted above as required by FWA00006790 (University of Pittsburgh), FWA00006735 (University of Pittsburgh Medical Center), FWA00000600 (Children's Hospital of Pittsburgh), FWA00003567 (Magee-Womens Health Corporation), FWA00003338 (University of Pittsburgh Medical Center Cancer Institute).

Please be advised that your research study may be audited periodically by the University of Pittsburgh Research Conduct and Compliance Office.

APPENDIX C

STUDY PARTICIPANT CONSENT FORM FOR WEST VIRGINIA SITES

University of Pittsburgh
Institutional Review Board
Approval Date: March 5, 2008
Renewal Date: March 4, 2009
IRB #: 0506048

CONSENT TO BE A SUBJECT IN A RESEARCH STUDY

TITLE: **University of Pittsburgh: Coordinating Center for Genetic Factors Contributing to Oral Health Disparities in Appalachia**

PRINCIPAL INVESTIGATOR: Mary L. Marazita, Ph.D., F.A.C.M.G.
Professor, Oral/Maxillofacial Surgery; Assoc. Dean of Research
School of Dental Medicine, University of Pittsburgh
Suite 500 Cellomics Building/100 Technology Drive
Pittsburgh, PA 15219 USA
Telephone: 412-648-8380

CO-INVESTIGATORS: Robert J. Weyant, D.M.D., Ph.D.
Head, Division of Pediatric and Developmental Dental Sciences
School of Dental Medicine, University of Pittsburgh
Pittsburgh, PA 15261
Telephone: 412-648-3076

Katherine Neiswanger, Ph.D.
Ph.D. Medical Geneticist
School of Dental Medicine, University of Pittsburgh
Suite 500 Cellomics Building, 100 Technology Drive
Pittsburgh, PA 15219 USA
Telephone: 412-648-8384

[SITE COORDINATOR]
[NAME]
[ADDRESS]
[PHONE]

SOURCE OF SUPPORT: National Institute of Dental and Craniofacial Research, U.S.A.

Why is this research being done?

Dr. Marazita and Dr. Weyant invite you to be in a study to learn more about dental health in families, including behaviors, genes (those factors that determine a person's physical characteristics and have been passed to them from their parents), and periodontal (gum tissue) factors. Oral health varies greatly among different people. The purpose of this study is to identify which genes, attitudes, and behaviors play a role in people's oral health, factors for oral health problems can be better understood.

Who is being asked to take part in this research study?

You are a member of one of approximately 700 families from West Virginia or Western Pennsylvania with at least one child between 1 and 18 years old, who is being asked to participate in this study. Your family is part of a representative sample of similar families in [NAME OF] County.

What procedures are being performed for research purposes?

You and your family will be asked to participate in a 4-part examination process during this visit. You and your family will also be asked to return every two years, for a total of three or four visits over five to seven years. If you agree to participate, you will undergo the following procedures during this visit. You have the right to participate in only one, two, three, or all four parts of the examination:

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Part 2) Dental, Microbiological and Tobacco Examinations: You will be given a dental screening to document the presence of oral conditions, including dental decay (cavities), gum infections (called gingivitis and periodontitis by dentists), tooth alignment and crowding, dental or oral injury, and a variety of other conditions of the teeth and mouth (for example, thin enamel). The dental exam will be conducted by a licensed dentist or dental hygienist and is similar to a routine checkup visit to a family dentist, except no x-rays will be taken. During this exam, you will be asked questions regarding your dental status, such as history of tooth injury, and brushing and flossing habits. All people have different kinds of bacteria present in their

mouth, so the purpose of the oral microbiological exam is to test your saliva ("spit") and the plaque on your teeth for bacteria that could cause cavities or gum infections. For this examination, you will provide a saliva sample by chewing on a wax pellet and then spitting into a vial. You will have a test to check the flow of your saliva. Your saliva will also be used to check if there is any evidence of tobacco use. A plastic strip will be placed on your tongue to collect saliva. The inside of your cheek may also be scraped to collect a sample. Dental instruments and special toothpicks will be used to scrape and collect dental plaque from your teeth and tongue. A long Q-tip will be used to collect a throat swab from the back of your throat. If any dental problems are found, you will be given referral information and can seek dental care at your own expense. Dental care will not be provided as part of this study. This part of the study will take about 1 hour.

Part 3) Blood sample for DNA studies: Approximately one and one half teaspoons blood will be used to evaluate your DNA for genes relating to dental health, such as those which affect cavities, tooth development, or wound healing. If you are unwilling to give a blood _____ have the option of providing a saliva (spit) sample or having the inside of your chee with several cotton swabs to collect cells that contain DNA. If necessary, you could —— provided some mouthwash to rinse to collect the DNA. This part of the study will take 5 minutes or less, and will only be done at one visit, unless the sample is insufficient to complete the study.

Part 4) Water Sampling: You have been sent a vial to collect a sample of your drinking water from your home. This water will be tested for fluoride, a mineral in some people's water that can prevent cavities. Please bring this vial with you to your appointment.

What are the possible risks, side effects, and discomforts of participating in this research study?

1) The questions in the interviews and questionnaires may be personal. If any information about child abuse, neglect, or mistreatment is uncovered, then the law requires that it be reported.

2) The dental screening infrequently causes some slight gum bleeding, which usually stops within a few minutes. If you have a serious gum infection, you may be sensitive to the gum examination. There is a rare risk that probing your gums may cause an abscess, or infection, of the gum tissue. Although this is rare and usually goes away within a short period of time, it might be painful and require treatment with antibiotics.

3) The gum examination is usually not a risky procedure for most healthy people. But, if you have had previous bacterial (infective) endocarditis, certain specific and serious congenital (present from birth) heart conditions, or artificial heart valves or have had a knee or hip replaced, this examination could place you at risk for a bacterial infection that would affect your heart and the joints in your bones. You will be asked if you have ever had any of these heart or joint problems, and if so, you will be asked to obtain and take an antibiotic (either amoxicillin or clindamycin, azithromycin, or clarithromycin) at your own expense an hour before the gum examination.

If you have the reduced ability to resist infection, this examination could place you at risk for developing an infection. If you have the reduced ability to form blood clots, you could be at risk for mild, but prolonged bleeding during some of the exam procedures. Prior to the dental exam, you will be asked in detail about having either of these conditions. If you have a reduced ability to resist infection or form blood clots, you will be excused from all parts of the examination that might cause bleeding.

4) Collection of tooth plaque, as well as the tongue and cheek scrapings, is likely to be briefly uncomfortable. The throat swab will likely lead to a brief gagging response.
5) The needle puncture of your vein to obtain the blood sample may infrequently result in pain and soreness, bruising, fainting, and rarely infection. This procedure will be performed by individuals trained and experienced in obtaining blood samples so as to minimize these risks.
6) In the unlikely event of a breach of confidentiality, there is a very remote possibility that the genetic information could affect your ability to be insured, employed, or your family relationships. Such problems are probably rare. You can ask the investigators about the likelihood of the research discovering anything that would lead to these problems.

What are the possible benefits of participating in this research study?

By participating, you may learn more about your own dental and overall health. You will receive verbal and written feedback about your dental screening. If your dental screening reveals any significant problems, you will also receive names of some dentists or other health professionals who could help with any related dental/medical needs. The informati
from your participation in this research study may eventually lead to a better unders
better treatments for oral health problems.

If I agree to take part in this research study, will I be told of any new risks that may be found during the course of this study?

You will be promptly notified if any new information develops during the conduct of this research study, which may cause you to change your mind about continuing to participate.

Will I or my insurance company be charged for the cost of any procedures performed as part of this research study?

If you are required to obtain the prophylactic antibiotic from your family doctor, you or your insurance will be charged the cost of the antibiotic. The study will reimburse any costs that you pay out-of-pocket to obtain the antibiotic.

Will I be paid if I take part in this research study?

You will be paid $5.00 for each procedure of the study that you complete, with an added $5.00 if all four procedures are completed, up to $25.00 for one visit. Each time you return for the study (every 2 years for a total of 3 or 4 visits), you will be paid these same amounts. Over a 5 – 7 year period, you could potentially receive $75 - $100 dollars depending on the total number of visits. You will also be reimbursed for any out-of-pocket expenses, including long distance communication, transportation, parking, one meal, prophylactic antibiotics, and any costs of obtaining a blood sample at a local lab.

Who will pay if I am injured as a result of taking part in this study?

University of Pittsburgh researchers recognize the importance of your voluntary participation in their research studies. These individuals and their staffs will make reasonable efforts to minimize, control, and treat any injuries that may arise as a result of this research. If you believe that you are injured as a result of the research procedures being performed, please contact immediately the Principal Investigator listed on the first page of this form.

Emergency medical treatment of injuries solely and directly related to your participation in this research study will be provided to you by the hospitals of UPMC. It is possible that UPMC may bill your insurance provider for the costs of this emergency treatment, but none of these costs will be charged directly to you. If your research-related injury requires medical care beyond this emergency, you will be responsible for the costs of this follow-up care unless otherwise specifically stated. There is no plan for monetary compensation. You do not, however, waive any legal rights by signing this form.

Who will know about my participation in this research study?

Any information obtained about you from this research study will be kept as confidential as possible. All information about you or your involvement in this research study will only be accessible to the investigators involved in this study and their research staff, and will not be released to anyone without your written permission. Records and information pertaining to your identity and involvement in this research study will be stored in locked file cabinets at the [School of Dentistry of the University of Pittsburgh OR LOCAL SITE]. Computer records will be kept in password protected, secured databases. Your identity on data records, and dental samples, and DNA will be indicated only by code number. Records lir to your personal identifying information will be stored in a separate, secure loca not be identified by name in any publication of the research results unless you sign a separate form giving your permission.

Will this research study involve the use or disclosure of my identifiable medical information?

This research study will NOT involve the use or disclosure of your identifiable medical information from your hospital or physician records, or future medical information that might become available during your participation in this study. This study will record some of your personal health or medical information, which will be kept separate from your medical records, and used only for research purposes.

Who will have access to identifiable information related to my participation in this research study?

The information learned about you during this study will not be released to anyone (for example, relatives, personal physicians, insurance companies, or any other third party) without your prior written permission. However, in the unlikely event that an interviewer identifies someone who is considered to be at immediate risk for harming him or herself or others, they will need to inform the appropriate agencies, as required by Pennsylvania law. Any information about child abuse, neglect, or mistreatment must also be reported. These research records, just like hospital records, may be subpoenaed by court order or may be inspected by federal regulatory authorities. In addition to the investigators listed on the first page of this consent form and their research staff, the following individuals may have access to identifiable information related to your participation in this research study. Authorized representatives of the University of Pittsburgh Research Conduct and Compliance Office may review your identifiable research information for the purpose of monitoring the appropriate conduct of this research study. In addition, authorized representatives of the University of Pittsburgh may have access to this information for the purpose of making participant payments.

For how long will the investigators be permitted to use identifiable information related to my participation in this research study?

The investigators may continue to use identifiable information related to your participation in this research study for at least 5 years following the completion of the research study.

May I have access to my personal research information resulting from my participation in this research study?

You will be notified if you have any dental problems. You will not be provided with your personal research or genetic information obtained during this study.

Is my participation in this study voluntary?

Your participation in this research study is completely voluntary. Whether or not you provide your consent for participation in this research study will have no effect on your current or future medical care at a UPMC Hospital or affiliated health care provider, or your current or future relationship with a health care insurance provider or with the University of Pittsburgh. If you turn 18 during the course of the study, your parent's permission is no longer valid, and vou will be re-contacted to give permission as an adult.

May I withdraw, at a future date, my consent for participation in this research study?

You do not have to take part in this study and, should you change your mind, you can withdraw from the study at any time by submitting a dated, written request to withdraw to Dr. Marazita, who is listed on page 1 of this form. Any research information recorded before your withdrawal may continue to be used in the research study. Your decision to withdraw from this research study will have no effect on your current or future medical care at a UPMC Hospital or affiliated health care provider, or your current or future relationship with a health care insurance provider or with the University of Pittsburgh. You may be removed from the study by the investigators, if the information you provide is incorrect. If you withdraw or are removed from this research study, your biological samples, blood sample, and DNA will be destroyed.

Will my DNA samples be used for future studies?

Dr. Marazita will control the use of your biological samples and genetic material for this study, and will store your biological samples with codes in freezers at the University of Pittsburgh and West Virginia University. In the future, new research may identify other factors that could be involved in oral health. If this happens, Dr. Marazita would also like to examine them. Thus, if you agree, your biological samples and DNA will be saved for future testing of newly identified factors involved in oral health. When all of her research studies of oral health are completed, any remaining biological samples and DNA will be destroyed at that time. If you do NOT agree, your biological samples and DNA will be discarded at the end of this particular research study. You may also be contacted in the future to be invited to participate in additional research, but that future involvement is voluntary as well. If you turn 18 during the course of the study, your parent's permission is no longer valid, and you will be re-contacted to give permission as an adult regarding the use of your DNA samples.

Your blood sample and its DNA used in this research study may contribute to a new invention or discovery. Sometimes, these inventions or discoveries may be of commercial value and may be sold, patented, or licensed by the investigators and the University of Pittsburgh for use in other

research or the development of new products related to oral health. If the research investigators are able to develop new products from the use of your biological sample or genetic material, they currently have no plans to share any money or other rewards with you. You retain the right to have your blood sample and its DNA destroyed if you decide to withdraw from this research study.

****

I give my permission for Dr. Marazita to save my biological samples and genetic material, with personal identifiers, for use in other genetic research projects involving the study of oral health.

YES _____ NO _____

I give my permission to be re-contacted to obtain my consent if there is a desire to use my biological sample or genetic material, with personal identifiers, in other research projects involving the study of different diseases or conditions.

YES _____ NO _____

_____

____

VOLUNTARY CONSENT AND AUTHORIZATION

All of the above has been explained to me and all of my current questions have been answered. I understand that I am encouraged to ask additional questions at any time about this research study, and that such future questions will be answered by the researchers listed on the first page of this form. Any questions I have about my rights as a research participant will be answered by the Human Subject Protection Advocate of the IRB Office, University of Pittsburgh (1-866-212-2668).

By signing this form, I agree to participate in this research study. A copy of this consent form will be given to me.

Adults aged 18 and over:

_____ _____

Participant's Signature Date

Children aged 1 – 17:

I understand that, as a minor (age less than 18 years), _____ is not permitted to participate in this research study without my consent. Therefore, by signing this form, I give my consent for their participation in this research study.

_____ _____
Parent's Name Relationship to Participant (Child)

_____ _____
Parent's Signature Date

Children who can sign their name:

This research has been explained to me, and I agree to participate.

_____
Child's Name

_____ _____
Child's Signature Date

Verification of explanation for children who can sign their name:

I certify that I have carefully explained the nature and purpose of this research study to the above-named child in age-appropriate language. They have had an opportunity to discuss it with me in detail. I have answered all their questions, and they have provided assent to participate in this study.

_____ _____
Printed Name of Person Obtaining Consent Role in Research Study

_____ _____
Signature of Person Obtaining Consent Date

All participants:

CERTIFICATION OF INFORMED CONSENT

I certify that the nature and purpose of this research study have been explained to the above-named individual(s), and the potential benefits and possible risks of study participation have been discussed. Any questions the individual(s) have about this study have been answered, and

we will always be available to address future questions as they arise. I further certify that no research component of this protocol was begun until after this consent form was signed.

_____
Investigator's Printed Name

_____ _____
Investigator's Signature Date

APPENDIX D

INSTITUTIONAL REVIEW BOARD APPROVAL LETTER FOR WEST VIRGINIA SITES

University of Pittsburgh

Institutional Review Board

3500 Fifth Avenue
Ground Level
Pittsburgh, PA 15213
(412) 383-1480
(412) 383-1508 (fax)

MEMORANDUM

TO: Mary Marazita, PhD

FROM: Christopher Ryan, PhD, Vice Chair

DATE: March 6, 2008

SUBJECT: IRB #0506048: University of Pittsburgh: Coordinating Center for Genetic Factors Contributing to Oral Health Disparities in Appalachia

---

Your renewal with modifications of the above-referenced proposal has received expedited review and approval by the Institutional Review Board under 45 CFR 46.110 (9).

Please include the following information in the upper right-hand corner of all pages of the consent form(s).

Approval Date: March 5, 2008
Renewal Date: March 4, 2009
University of Pittsburgh
Institutional Review Board
IRB #0506048

Please note that it is the investigator's responsibility to report to the IRB any unanticipated problems involving risks to subjects or others [see 45 CFR 46.103(b)(5) and 21 CFR 56.108(b)]. The IRB Reference Manual (Chapter 3, Section 3.3) describes the reporting requirements for unanticipated problems which include, but are not limited to, adverse events. If you have any questions about this process, please contact the Adverse Event Coordinator at 412-383-1504.

The protocol and consent forms, along with a brief progress report must be resubmitted at least **one month prior** to the renewal date noted above as required by FWA00006790 (University of Pittsburgh), FWA00006735 (University of Pittsburgh Medical Center), FWA00000600 (Children's Hospital of Pittsburgh), FWA00003567 (Magee-Womens Health Corporation), FWA00003338 (University of Pittsburgh Medical Center Cancer Institute).

Please be advised that your research study may be audited periodically by the University of Pittsburgh Research Conduct and Compliance Office.

CR:kh

APPENDIX E

SCREENING INTERVIEW FORM PART 1, 2, AND 3-4

34432

COHRA
Screening Interview Part 1.

COHRA

Screening ID | Date / / | Staff ID

Family Informant Information:

Last Name

First Name

Other names (maiden name)

Address (number, street)

City

State Zip Code

Home Phone Number:

☐ Check here if no home phone

Area Code Phone number

– –

In what ways have your heard about the project?

1.

2.

3.

4.

Did anyone refer you to our project? ○ No ○ Yes

If yes, who referred you?

34432

COHRA
Screening Interview Part 1.

COHRA

Screening ID	Date	Staff ID
	/ /	

Part 1. Informant Information

1.a What is your birth date? Month / Day / Year

1.b How old are you now? Years

2. Where were you born?

2.a If U.S.:

State City

2.b If not U.S.:

Country

3. What is your gender?
- O Male
- O Female

4. I would like to ask you some questions about your children.

4.a How many children do you have all together?

4.b How many of them are between 1 and 18 years old?

4.c How many of them live with you?

5. What is your race/ethnicity?
- O White
- O African American
- O Hawian/Pacific Islander
- O Hispanic
- O Native American or Alaskan Native
- O Asian
- O Other
- O Don't Know

6. What is the nationality of your grandparents? (Use nationality code or enter 88 if you don't know)

6.a –	Maternal Grandmother	6.e –	Paternal Grandmother
6.b –	(if needed)	6.f –	(if needed)
6.c –	Maternal Grandfather	6.g –	Paternal Grandfather
6.d –	(if needed)	6.h –	(if needed)

COHRA
Screening Interview Part 1.

COHRA

Screening ID	Date	Staff ID
	/ /	

6. Grandparents nationality Continued...

Notes:

7. How many years of education have you had altogether? (12 years = H.S. Graduate)

Total Years of Education

16367

COHRA
Screening Interview Part 2.

COHRA

Screening ID	Date	Staff ID
	/ /	

Part 2. Household Information

8. Where is your home located?

- O Nicholas County
- O Webster County
- O Other County--->If Other, please specify
- O Don't Know

8.a What is the nearest incorporated city or town?

8.b How many miles is it from your home to that city/town?

9. What type of community do you live in?

- O Rural/Farming/Mining
- O Unincorporated community
- O Other-----> If Other, please specify
- O Don't Know

10. Who is currently living with you in your home?

10.a Your spouse O No O Yes

10.b Your domestic partner O No O Yes

10.c Children, related to you or not O No O Yes If Yes how many?

10.d Your brothers or sisters O No O Yes If Yes how many?

10.e Your parents O No O Yes If Yes how many?

10.f Other relatives O No O Yes If Yes how many?

10.g Other unrelated individuals O No O Yes If Yes how many?

16367

COHRA
Screening Interview Part 2.

COHRA

Screening ID | Date __/__/____ | Staff ID ___

11. For each child under 18 living in your house, specify how that child is related to you:

Child 1 (Age)

__ __ ○ Month(s) ○ Year(s)

○ biological child
○ step child
○ adopted child
○ not my child, but biologically related---> specify
○ unrelated child----> specify

Child 2 (Age)

__ __ ○ Month(s) ○ Year(s)

○ biological child
○ step child
○ adopted child
○ not my child, but biologically related---> specify
○ unrelated child----> specify

Child 3 (Age)

__ __ ○ Month(s) ○ Year(s)

○ biological child
○ step child
○ adopted child
○ not my child, but biologically related---> specify
○ unrelated child----> specify

16367

COHRA
Screening Interview Part 2.

COHRA

Screening ID	Date	Staff ID
	/ /	

Child 4 (Age)

Month(s)
Year(s)

biological child
step child
adopted child
not my child, but biologically related---> specify
unrelated child----> specify

Child 5 (Age)

Month(s)
Year(s)

biological child
step child
adopted child
not my child, but biologically related---> specify
unrelated child----> specify

Child 6 (Age)

Month(s)
Year(s)

biological child
step child
adopted child
not my child, but biologically related---> specify
unrelated child----> specify

16367

COHRA
Screening Interview Part 2.

COHRA

Screening ID | Date / / | Staff ID

Child 7 (Age)

O Month(s)
O Year(s)

O biological child
O step child
O adopted child
O not my child, but biologically related---> specify
O unrelated child----> specify

Child 8 (Age)

O Month(s)
O Year(s)

O biological child
O step child
O adopted child
O not my child, but biologically related---> specify
O unrelated child----> specify

12. How long have you lived in this household arrangement? years

13. How many vehicles do the people in your household have all together?

14. What is the total yearly income for everyone in the household put togehter?

O Less than 10,000
O 10,000-14,999
O 15,000-24,999
O 25,000-34,999
O 35,000-49,000
O 50,000-74,999
O 75,000-99,999
O 100,000-149,999
O 150,000-199,999
O 200,000 or more
O Don't Know

COHRA
Screening Interview Part 2.

COHRA

Screening ID	Date	Staff ID
	/ /	

15. What are the total assets for everyone in the household?

(savings, investments, home, land, vehicles)

- O Less than 10,000
- O 10,000-14,999
- O 15,000-24,999
- O 25,000-34,999
- O 35,000-49,000
- O 50,000-74,999
- O 75,000-99,999
- O 100,000-149,999
- O 150,000-199,999
- O 200,000 or more
- O Don't Know

11173

COHRA
Screening Interview Parts 3-4

COHRA

Screening ID	Date	Staff ID
	/ /	

Part 3. Housing Information

16. What type of house do you live in?

- O Single family home
- O Duplex
- O Multiplex
- O Apartment
- O Single-wide mobile or modular home
- O Double-wide mobile or modular home
- O Other-----> If other please specify:
- O Don't Know

17. Do you own or rent?

- O Own
- O Rent
- O Don't know

18.a How many bedrooms do you have?

18.b How many bathrooms?

baths

half-baths

19. About how many square feet are there in your home?

20. What is your source of tap water?

- O Private/public water company
- O Private/public well
- O Other
- O Don't know

20.a Do you have flouride in your tap water?

- O Yes
- O No
- O Don't know

11173

COHRA
Screening Interview Parts 3-4

COHRA

Screening ID | Date / / | Staff ID

21. What is the source of heat for your home?

Electricity
O Yes O No O Don't know

LP gas (propane)
O Yes O No O Don't know

Natural gas
O Yes O No O Don't know

Wood
O Yes O No O Don't know

Coal
O Yes O No O Don't know

Other (Please specify)

22. What kind of sewage system does your home have?

O Septic tank O Don't know
O Public
O Other--->

If Other (Please specify)

23. What other utilities do you have?

23.a Telephone
O Yes
O No
O Don't know

23.b Television
O Yes
O No
O Don't know

23.c Cable Television
O Yes
O No
O Don't know

23.d Internet access
O Yes
O No
O Don't know

Other (Please specify)

24. What type of lot or land do you live on?

O Housing development/subdivision
O Lot for single-family home
O Lot for single-wide mobile or modular home
O Lot for double-wide mobile or modular home
O Farm
O Don't know
O Other

If Other (Please specify)

11173

COHRA
Screening Interview Parts 3-4

COHRA

Screening ID	Date	Staff ID
	/ /	

25. How much land do you live on?

- O Less than 1 acre---------->Specify approximate size 0.
- O At least 1 acre---> . Specify number of acres
- O Don't know

26. Do you own or rent the land you live on?

- O Own
- O Rent
- O Not applicable
- O Don't know

If not applicable please specify why

11173

COHRA
Screening Interview Parts 3-4

COHRA

Screening ID | Date | Staff ID

Part 4. Exclusion Questions

27.a Is there anyone in your household who has a reduced capacity to fight infections (e.g., with leukemia, cancer, unstable diabetes, taking corticosteroids or immunosuppressive therapy, HIV+, a transplant recipient, undergoing dialysis) or the reduced ability to form blood clots (due to a blood clotting disorder or is taking blood thinners such as coumadin or heparin)?

- O No
- O Yes
- O Suspects
- O Don't know

!!! If "**YES**" or "**SUSPECTS**": Staff family to decide whether individual or family should be excluded.

27.b Is there anyone in your household who has a heart problem or suspects they may have a heart problem that requires antibiotic pre-medication, has an artificial joint replacement, or needs to take an antibiotic before they have a dental exam?

- O No
- O Yes
- O Suspects *
- O Don't know

If "**YES**" or "**SUSPECTS**":

27.c Would they be willing to take an antibiotic (amoxicillin or clindamycin, azithromycin, or clarithromycin) before they have the dental exam in this studv?

- O No
- O Yes
- O Don't know

!!! If "**YES**" to 27.b and "**NO**"to 27.c: Staff family to decide whether individual or family should be excluded.

*If "**SUSPECTS**" to 27.b and "**NO**" to 27.c:

27.c Would they be willing to come in and sign a medical release so that we could contact their doctor to help determine if pre-medication is necessary?

- O No
- O Yes---------->
- O Don't know

AppointmentDate

Appointment Time: : O AM O PM

Appointment Location

APPENDIX F

DENTAL EXAMINATION FORM FOR AGE ≥ 18

COHRA Dental Examination

Age >=18

COHRA

Barcode ID

4.9. Trauma

Record anterior tooth trauma using the following codes:

Code criteria:

Class 1 – Simple fracture of the crown not involving dentin
Class 2 – Extensive fracture of the crown involving dentin
Class 3 - Extensive fracture of the crown involving dentin and pulp exposure
Class 4 – Teeth lost as result of trauma
Class 5 – Fracture of the root
Class 6 – Displacement of tooth (without fracture of crown or root)

Is there trauma to the maxillary anterior teeth?

Trauma

O Yes O No

CLASS

O 1
O 2
O 3
O 4
O 5
O 6

Is there trauma to the mandibular anterior teeth?

Trauma

O Yes O No

CLASS

O 1
O 2
O 3
O 4
O 5
O 6

4.10. Throat swab:

1. Check mouth for obstructing material; label swab container
2. Depress tongue with tongue blade
3. Vigorously swab posterior pharynx beyond uvula with swab for 2 seconds (cause gag reflex)
4. Place swab in labeled container; hold at room temperature until transport to WVU

Throat Swab

O Performed

O Not Performed - Refused

O Not Performed - Unable to collect

COHRA Dental Examination

Age >=18

COHRA

ELIGIBILITY CRITERIA

Exam	Age 1 to 6	Age 7 to 10	Ages 11-13 and 14-17	Age >=18
2.1. Blood samples	yes	yes	yes	yes
3.1. SUPRAginval plaque	yes	yes	yes	yes
3.1. tongue scraping	yes	yes	yes	yes
3.2. Stimulated saliva secretion rates	NO	yes	yes	yes
4.1. Soft tissue exam	yes	yes	yes	yes
4.2. Dentures assessment	yes	yes	yes	yes
4.3. Eligibility criteria	yes	yes	yes	yes
4.4. Bana Tongue scraping	yes	yes	yes	yes
4.4. BANA SUBgingival plaque	NO	*Yes if no need of prof	*Yes if no need of prof	yes
4.5. Papillary bleeding score	NO	*Yes if no need of prof	*Yes if no need of prof	yes
4.6. Periodontal screening	NO	NO	NO	yes
4.7. Maloccusion	NO	yes	yes	yes
4.8. Caries	yes	yes	yes	yes
4.9. Trauma	yes	yes	yes	yes
4.10. Throat swab	yes	yes	yes	yes
4.11. Clinical findings	yes	yes	yes	yes

* ONLY IF NO PRE-MED NEEDED

8705

COHRA Dental Examination

Age >=18

BARCODE

COHRA

Barcode ID	Date	Staff ID
	/ /	

2 - Blood samples

2.1. Blood sample

Blood samples are the first priority and should be attempted on all subjects. If not possible, Oragene Saliva samples or Cotton Swabs are the next option. Mouth Rinse is the final option.

Blood Sample

If a blood sample is performed, and a specimen is obtained for the patient records, **STOP** and proceed to Section 3.1. If a specimen is not obtained, go to Oragene Saliva Samples below. Record the results on the right.

- O Performed
- O Not Performed - Refused
- O Not Performed - Unable to collect

Oragene Saliva Sample

If sample is performed, record the appropriate response on the right. If not able to obtain sample then go to Cotton Swab section below.

- O Performed
- O Not Performed

Cotton Swabs

If a swab is performed, record the appropriate response on the right.

- O Performed
- O Not Performed

Mouth Rinse

If a mouth rinse is performed, and a specimen is collected for the patient records, **STOP** and proceed to Section 3.1. Record the results on the right.

- O Collected
- O Not Collected - Refused
- O Not Collected - Unable to collect
- O Not Collected - <= 6 years

COHRA Dental Examination

Age >=18

COHRA

Barcode ID	Date	Staff ID
	/ /	

3 - SAMPLING / LAB

3.1 Supragingival plaque samples:

- Take samples and place it inside the Eppendorff tubes filled with buffer.

- Take plaque from multiple teeth using the same instrument, change instrument between sample type

☐ **Sample 1: Surface of intact enamel (sound)** → **Use stimudent**

☐ **Sample 2: Surface of white spot lesion**

☐ **Sample 3: Surface of cavitated initial enamel lesions** → **Use Gracey curretes**

☐ **Sample 4: Excavated dentin from deep dentin lesions**

☐ **Sample 5: Tongue Scraping** → **Use stimudent**

COHRA Dental Examination

Age >=18

COHRA

Barcode ID

3.2. Stimulated saliva secretion rate

Procedure1: S Mutans:

Obs: Give to the particiant a paraffin pellet and ask them to chew it for one minute.

Collection Date: __/__/____

Collection Time: __:__ O AM O PM

Reading Date: __/__/____

Reading Time: __:__ O AM O PM

Test Result (choose one)

- O 0
- O 1
- O 2
- O 3
- O Performed, but test failed
- O Not Performed
- O Not Performed - Refused

Comments:

Procedure2: Measurements of stimulated Salivary Flow Secretion Rate (3 min)

Obs: pre-weigh the tube BEFORE collecting the saliva

Total tube weight __.__ grams

Total Saliva PLUS tube weight __.__ grams

- O Not Performed
- O Not Performed - Refused

→ If no saliva fill in the box with 0.00

Comments:

PRESERVE THE SALIVA FOR THE NEXT TEST (cotinine)

COHRA Dental Examination

Age >=18

COHRA

Barcode ID

3.2.C Cotinine (Chairside):

- ○ 1
- ○ 2
- ○ 3
- ○ 4
- ○ 5
- ○ 6
- ○ Negative
- ○ Not Performed

Comments:

COHRA Dental Examination

Age >=18

COHRA

Barcode ID

Oral, dental, perio examination

4.1. SOFT TISSUES EXAM (Examiner note: Mark all positive findings and comment. If no positive findings, mark "No positive findings.")

Definitive Diagnosis:

- ☐ 1. Herpes Labialis
- ☐ 2. Angular Cheilitis
- ☐ 3. Actinic Cheilitis
- ☐ 4. Gingivitis Localized
- ☐ 5. Gingivitis Generalized
- ☐ 6. Gingival Hyperplasia
- ☐ 7. Migratory Glossitis
- ☐ 8. Median Rhomboid Glossitis
- ☐ 9. Atrophy of Tongue Papillae
- ☐ 10. Fissured Tongue
- ☐ 11. Fistulous Tract
- ☐ 12. Pseudomembranous Candidasis
- ☐ 13. Denture Stomatitis
- ☐ 14. Epulus Fissuratum
- ☐ 15. Parotid Enlargement
- ☐ 16. Inflammatory Papillary Hyperplasia
- ☐ 17. Apthous Ulcer
- ☐ 18. Traumatic Ulcer
- ☐ 19. Herpetic Ulcer
- ☐ 20. Lichen Planus
- ☐ 21. Erosive Lichen Planus
- ☐ 22. Papilloma
- ☐ 23. Fibroma/Irritation Fibroma
- ☐ 24. No Positive Findings
- ☐ 25. Other Diagnosis Description

COHRA Dental Examination

Age >=18

COHRA

Barcode ID

4.2. Dentures

Is the participant wearing dentures (either partial or full)?

Upper Dentures	**Lower Dentures**
O Full Upper	O Full Lower
O Partial Upper	O Partial Lower
O None Upper	O None Lower

4.2.a. Orthodontic Appliance

Is the participant currently wearing braces?

O Yes O No

Does the participant have a retainer or a removable appliance?

O Yes O No

4.3. Eligibility criteria for edentulous patients:

Is participant completely edentulous?

O Yes O No

If yes, stop here and perform:

4.4. **BANA test** (tongue scraping ONLY)
4.10. **Throat swab**

COHRA Dental Examination

Age >=18

COHRA
Barcode ID

4.4 Subgingival plaque and tongue scraping for BANA test

BANA tongue scraping:

- O Performed
- O Not Performed

BANA Result:
- O Negative
- O Weak Positive
- O Positive

Subgingival plaque: BANA subgingival and subgingival plaque(DNA analysis):

Does the participant need PRE-MED?

O Yes O No

If yes, stop here and GO TO 4.7. MALOCCLUSION EXAM

METHODS for BANA subgingival and subgingival plaque(DNA analysis):

Sample all first molars. If not present, sample the next most posterior tooth, excluding 3rd molars.

Use a cotton roll or a scaler to clean supragingival plaque before taking subgingival plaque samples

Perform periodontal screening PSR on all sites sampled for BANA.

Use a sterile PSR probe for each site.

Procedures:

1- Collect all 4 subgingival plaque samples for BANA and incubate the BANA strip

2- Collect all 4 subgingival plaque samples for DNA analysis and place inside the tubes containing the buffer

3- Using 4 sterile PSR probes (ONE FOR EACH SITE), perform the PSR score for all teeth sampled

8705

COHRA Dental Examination

Age >=18

COHRA

Barcode ID

1. BANA TEST:

3 Mesio-Buccal

Fill in a tooth number **ONLY** If tooth not present please indicate bellow the tooth examined (most posterior adjacent):

Tooth Number → **Tooth Site**: O Mesial O Lingual O Distal O Occlusal O Buccal →

O Negative
O Weak Positive
O Positive
O Not Performed

2. Subgingival plaque:

Subgingival plaque collected O Yes O No

3. PSR score:

O 1 O 2 O 3

Recession: O Yes O No

Bleeding: O Yes O No

1. BANA TEST:

14 Mesio-Buccal

Fill in a tooth number **ONLY** If tooth not present please indicate below the tooth examined (most posterior adjacent):

Tooth Number → **Tooth Site**: O Mesial O Lingual O Distal O Occlusal O Buccal →

O Negative
O Weak Positive
O Positive
O Not Performed

2. Subgingival plaque:

Subgingival plaque collected O Yes O No

3. PSR score:

O 1 O 2 O 3

Recession: O Yes O No

Bleeding: O Yes O No

8705

COHRA Dental Examination

Age >=18

COHRA

Barcode ID

1. BANA TEST:

19 Mesio-Buccal

Fill in a tooth number **ONLY** If tooth not present please indicate below the tooth examined (most posterior adjacent):

Tooth Number → **Tooth Site**: O Mesial O Lingual O Distal O Occlusal O Buccal →

- O Negative
- O Weak Positive
- O Positive
- O Not Performed

2. Subgingival plaque:

Subgingival plaque collected O Yes O No

3. PSR score:

O 1 O 2 O 3

Recession: O Yes O No

Bleeding: O Yes O No

1. BANA TEST:

30 Mesio-Buccal

Fill in a tooth number **ONLY** If tooth not present please indicate below the tooth examined (most posterior adjacent):

Tooth Number → **Tooth Site**: O Mesial O Lingual O Distal O Occlusal O Buccal →

- O Negative
- O Weak Positive
- O Positive
- O Not Performed

2. Subgingival plaque:

Subgingival plaque collected O Yes O No

3. PSR score:

O 1 O 2 O 3

Recession: O Yes O No

Bleeding: O Yes O No

COHRA Dental Examination

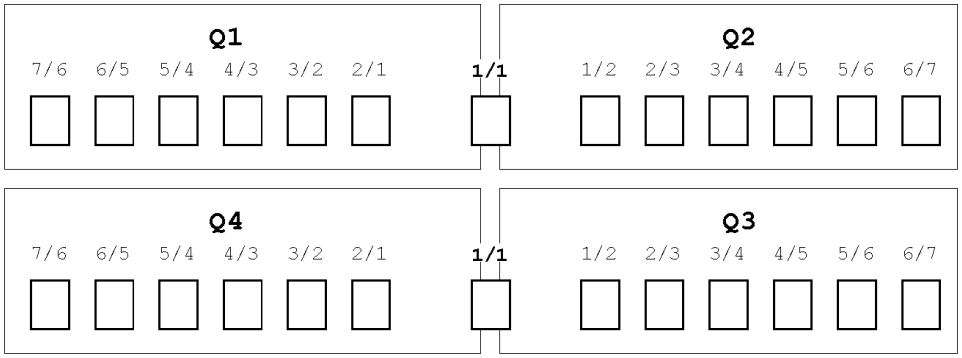
Age >=18

COHRA

Barcode ID

4.5. Papillary Bleeding Score

O Performed O Not Performed O Not Performed - Refused



0 = healthy gingiva; no bleeding upon insertion of STIMUDENT inter-proximally

1 = edematous, reddened gingiva; no bleeding upon insertion of STIMUDENT inter-proximally

2 = bleeding without flow along gingival margin upon insertion of STIMUDENT inter-proximally

3 = bleeding with flow along gingival margin upon insertion of STIMUDENT inter-proximally

4 = copious bleeding upon insertion of STIMUDENT inter-proximally

5 = severe inflamation, marked redness and edema; tendency to spontaneous bleeding

9 = missing at least one of pair teeth

8705

COHRA Dental Examination

Age >=18

COHRA

Barcode ID

4.6.Periodontal screening: PSR

S1 Edentulous O yes

O 1 O 2 O 3

Recession: O Yes O No

Bleeding: O Yes O No

S4 Edentulous O yes

O 1 O 2 O 3

Recession: O Yes O No

Bleeding: O Yes O No

S2 Edentulous O yes

O 1 O 2 O 3

Recession: O Yes O No

Bleeding: O Yes O No

S5 Edentulous O yes

O 1 O 2 O 3

Recession: O Yes O No

Bleeding: O Yes O No

S3 Edentulous O yes

O 1 O 2 O 3

Recession: O Yes O No

Bleeding: O Yes O No

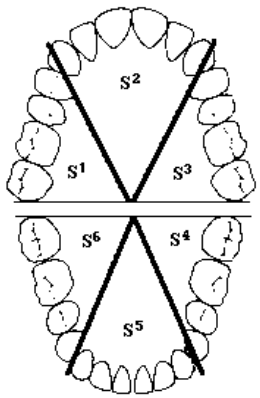
S6 Edentulous O yes

O 1 O 2 O 3

Recession: O Yes O No

Bleeding: O Yes O No

PSR	Deepest probing depth in sextant
1	Less than 3.5 mm
2	More than 3.5 mm but less than 5.5.mm
3	More than 5.5 mm



8705

COHRA Dental Examination

Age >=18

COHRA

Barcode ID

***PLEASE ASK PATIENT TO BRUSH HIS/HER TEETH AT THIS POINT

4.7. Maloccusion exam:

Feature	Technique	First measure		Second measure	
Overjet	Place probe perpendicular to the facial surface of the mandibular central incisor and measure the point where the maxillary incisor contacts the probe.	More than white band	O Yes	If yes, is it greater than white plus black band?	O Yes O No
			O No	If no, is there a reverse overjet?	O Yes O No
Open Bite	Measure open bite at maximal point by placing the probe at the black band region along the facial/buccal surface	More than black band	O Yes	If yes, is it more than the white band?	O Yes O No
			O No		
Displacement	Measures the largest tooth displacement using the black band area of the probe. Use either the full black plus white portion for larger displacements.	More than black band	O Yes	If yes, is it more than the white band?	O Yes O No
			O No		
Over Bite	Visually determine if maxillary incisor covers completely the mandibular incisor. Also indicate if there is palatal trauma from deep overbites.	Complete	O Yes	If yes, is there tissue damage?	O Yes O No
			O No		
Angles class	O Class 1 O Class 2 O Class 3				

COHRA Dental Examination

Age >=18

COHRA

Barcode ID

4.8. Caries exam:

Coronal and root caries will be diagnosed using the following codes:

Surface Status	Code	Condition/Severity
Missing	01	Trauma
Missing	02	Ortho
Missing	03	Other
Missing	31	Other Decay
Missing	32	Other Perio
Missing	33	Other Unerupted
Missing	04	Pontic
Missing	41	Pontic Decay
Missing	42	Pontic Perio
Missing	43	Pontic Unerupted
Missing	05	Implants
Missing	51	Implants Decay
Missing	52	Implants Perio
Missing	53	Implants Unerupted
Healthy/Sound	06	Sound
Healthy/Sound	07	Sealed
Healthy/Sound	08	Stain
Healthy/Sound	09	Fluorosis
Healthy/Sound	10	Hypoplasia
Decay	11	White spot
Decay	12	Cavitation in enamel
Decay	13	Cavitation in dentin
Decay	14	Pulp exposure
Decay	15	Decay/recurrent
Restored	16	Restored
Root caries		Yes/No

8705

COHRA Dental Examination

Age >=18

COHRA

Barcode ID

Quadrant 1/ MAXILLARY TEETH

	Sound 2	Sound 3	Sound A/4	Sound B/5	Sound C/6	Sound D/7	Sound E/8
	O PRIM O PERM	O PRIM O PERM	O PRIM O PERM	O PRIM O PERM	O PRIM O PERM	O PRIM O PERM	O PRIM O PERM
M	M	M	M	M	M	M	M
M					99	99	99
O							
D							
B							
L							
Root caries	Root caries	Root caries	Root caries	Root caries	Root caries	Root caries	Root caries
	O Yes O No	O Yes O No	O Yes O No	O Yes O No	O Yes O No	O Yes O No	O Yes O No

Quadrant 2/ MAXILLARY TEETH

	Sound F/9	Sound G/10	Sound H/11	Sound I/12	Sound J/13	Sound 14	Sound 15
	O PRIM O PERM	O PRIM O PERM	O PRIM O PERM	O PRIM O PERM	O PRIM O PERM		
M	M	M	M	M	M	M	M
M	99	99	99				
O							
D							
B							
L							
Root caries	Root caries	Root caries	Root caries	Root caries	Root caries	Root caries	Root caries
	O Yes O No	O Yes O No	O Yes O No	O Yes O No	O Yes O No	O Yes O No	O Yes O No

8705

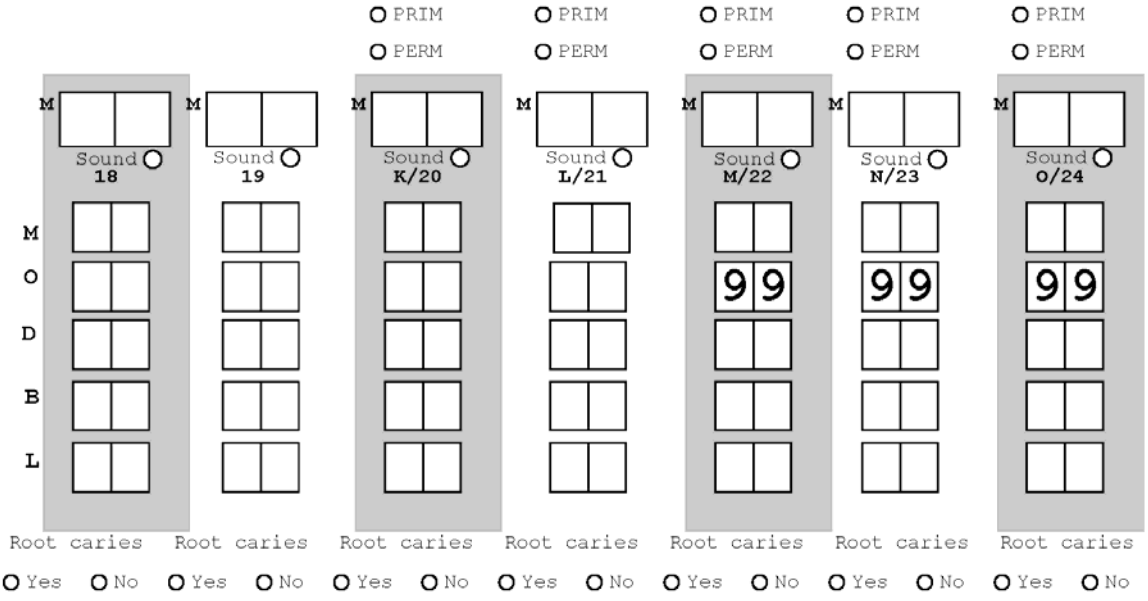
COHRA Dental Examination

Age >=18

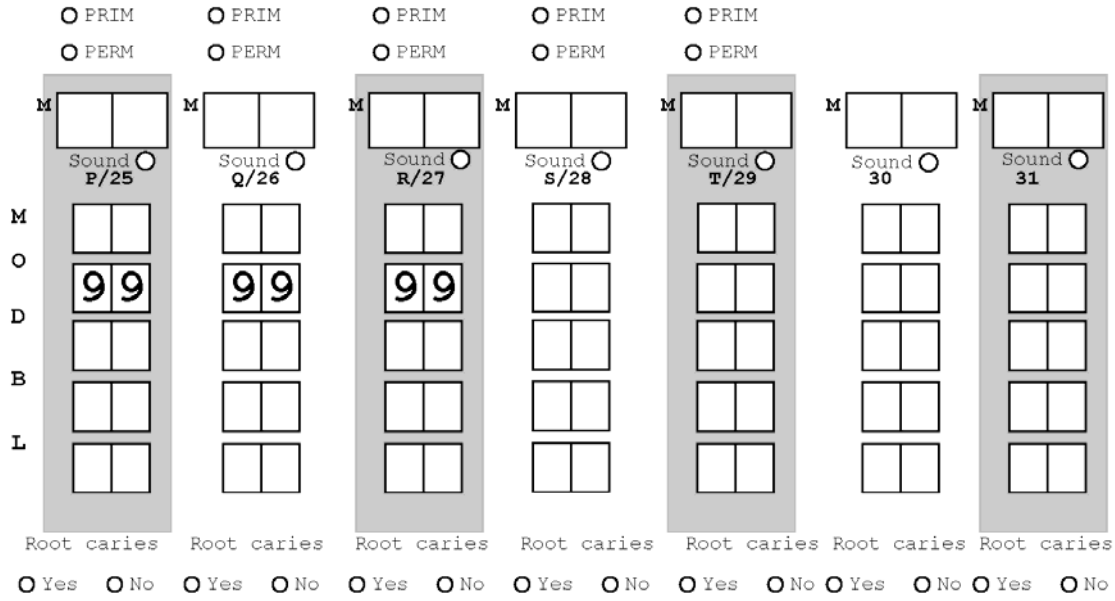
COHRA

Barcode ID

Quadrant 3/ MANDIBULAR TEETH



Quadrant 4/ MANDIBULAR TEETH



APPENDIX G

DENTAL EXAMINATION SUPPLEMENT FORM

58038

COHRA Dental Examination

Supplement Form

Barcode ID

COHRA

Supragingival plaque S. Mutans

Procedure: S Mutans:

Obs: Take samples as described, put on the Dentocult strip at positions 1-4

Collection Date: ☐☐/☐☐/☐☐☐☐

Collection Time: ☐☐:☐☐ ○ AM ○ PM

Sample 1: Surface of intact enamel (sound)

Test Result (choose one)
- ○ 0
- ○ 1
- ○ 2
- ○ 3
- ○ Performed, but test failed
- ○ Not Performed
- ○ Not Performed - Refused

Sample 2: Surface of white spot lesion

Test Result (choose one)
- ○ 0
- ○ 1
- ○ 2
- ○ 3
- ○ Performed, but test failed
- ○ Not Performed
- ○ Not Performed - Refused

Sample 3: Surface of cavitated initial enamel lesions

Test Result (choose one)
- ○ 0
- ○ 1
- ○ 2
- ○ 3
- ○ Performed, but test failed
- ○ Not Performed
- ○ Not Performed - Refused

Sample 4: Excavated dentin from deep dentin lesions

Test Result (choose one)
- ○ 0
- ○ 1
- ○ 2
- ○ 3
- ○ Performed, but test failed
- ○ Not Performed
- ○ Not Performed - Refused

Comments:

APPENDIX H

ALL RESULTS

	PlaqSam1:PlaqSam1			PlaqSam1:PlaqSam2		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	370	369.1	0.12 *	370	369.6	0.04
Parent:Offspring	2054	1430.5	-0.01	2054	1321.1	-0.07 *
Sibling	885	565	0.23 ***	885	832.6	0.04
Half-Sibling	271	195.4	0.18 *	271	354.1	0.01
	PlaqSam1:PlaqSam3			PlaqSam1:PlaqSam4		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	370	368.9	-0.01	370	368.4	0.02
Parent:Offspring	2054	1479.5	-0.11 ***	2054	1398.5	-0.12 ***
Sibling	885	976.4	0.02	885	939.4	-0.03
Half-Sibling	271	376.5	-0.003	271	342.2	-0.04
	PlaqSam1:PlaqSam5			Plaqsam2:PlaqSam1		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	370	369	-0.03	370	367.7	0.08
Parent:Offspring	2054	1566.9	0.01	2054	1239.1	-0.04
Sibling	885	793	0.16 ***	885	832.6	0.04
Half-Sibling	271	276.5	0.144 *	271	354.1	0.01
	PlaqSam2:PlaqSam2			PlaqSam2:PlaqSam3		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	370	369.6	0.37 ***	370	369.4	0.20 ***
Parent:Offspring	2054	1162.6	0.23 ***	2054	1290.1	0.07 *
Sibling	885	489.9	0.33 ***	885	811.2	0.12 ***
Half-Sibling	271	187	0.08	271	335.1	0.1

	PlaqSam2:PlaqSam4			PlaqSam2:PlaqSam5		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	370	368.4	0.09	370	369.9	0.06
Parent:Offspring	2054	1214.7	-0.05	2054	1358.5	-0.05
Sibling	885	822.5	0.11 ***	885	943.4	-0.02
Half-Sibling	271	344.2	0.03	271	389.7	0.003
	PlaqSam3:PlaqSam1			PlaqSam3:PlaqSam2		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	370	368.6	0.03	370	369	0.20 ***
Parent:Offspring	2054	1320.1	0.05	2054	1225.8	0.11
Sibling	885	976.4	0.02	885	811.2	0.12 ***
Half-Sibling	271	376.5	-0.003	271	335.1	0.1
	PlaqSam3:PlaqSam3			PlaqSam3:PlaqSam4		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	370	369.4	0.24 ***	370	369.9	0.13 *
Parent:Offspring	2054	1392.8	0.14 ***	2054	1304.9	0.002
Sibling	885	585.4	0.20 ***	885	914.5	0.11 ***
Half-Sibling	271	210.1	0.09	271	342	0.07
	PlaqSam3:PlaqSam5			PlaqSam4:PlaqSam1		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	370	365.2	0.11 *	370	368	-0.04
Parent:Offspring	2054	1256.9	0.02	2054	1327.5	0.02
Sibling	885	1090.7	0.01	885	939.4	-0.03
Half-Sibling	271	411.3	-0.02	271	342.2	-0.04
	PlaqSam4:PlaqSam2			PlaqSam4:PlaqSam3		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	370	369.4	0.07	370	368.2	0.15 **
Parent:Offspring	2054	1227.8	0.04	2054	1386.1	0.05
Sibling	885	822.5	0.11 ***	885	914.5	0.11 ***
Half-Sibling	271	344.2	0.03	271	342	0.07
	PlaqSam4:PlaqSam4			PlaqSam4:PlaqSam5		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	370	369.3	0.24 ***	370	369.6	-0.02
Parent:Offspring	2054	1304.7	0.07 **	2054	1463.3	-0.01
Sibling	885	555.6	0.24 ***	885	1055.3	-0.05
Half-Sibling	271	192.1	0.21 **	271	380.9	-0.05
	PlaqSam5:PlaqSam1			PlaqSam5:PlaqSam2		

	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	370	369	-0.03	370	367.7	0.1
Parent:Offspring	2054	1559.9	0.002	2054	1444	0.02
Sibling	885	793	0.16 ***	885	943.4	-0.02
Half-Sibling	271	276.5	0.144 *	271	389.7	0.003
	PlaqSam5:PlaqSam3			PlaqSam5:PlaqSam4		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	370	369.4	0.01	370	365.7	-0.10 *
Parent:Offspring	2054	1623.6	0.04	2054	1535.1	-0.05 *
Sibling	885	1090.7	0.01	885	1055.3	-0.05
Half-Sibling	271	411.3	-0.02	271	380.9	-0.05
	PlaqSam5:PlaqSam5					
	count	equiv count	correlation			
Mother:Father	370	369	-0.02			
Parent:Offspring	2054	1703.3	0.01			
Sibling	885	642.4	0.15 ***			
Half-Sibling	271	219.2	0.1			

*** 0.01 ≤ p ≤ 0.05**
**** 0.001 ≤ p ≤ 0.009**
***** p ≤ 0.0009**
Standard error range for correlation values included in table: 0.0242 – 0.0729

	TestR:TestR			TestR:SupTestR		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	359	357.9	-0.01	74	1.2	0.06 ***
Parent:Offspring	1051	1096.5	0.02	355	11.9	-0.08
Sibling	383	273.8	-0.03	96	41.6	0.01
Half-Sibling	93	93.3	-0.02	68	2.7	-0.04 ***
	TestR:SupTestR2			TestR:SupTestR3		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	21	1	0.18 ***	34	1	0.23 ***
Parent:Offspring	87	1.1	0.12 ***	94	1.1	0.13 ***
Sibling	26	1	0.19 ***^	25	8.3	-0.06
Half-Sibling	22	1.2	-0.11 ***	17	1.3	-0.18 ***
	TestR:SupTestR4			SupTestR:TestR		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	30	1	0.29 ***	68	8.5	-0.18
Parent:Offspring	55	1.1	0.15 ***	223	35.2	-0.03

Sibling	15	1	-0.07 ***	96	41.6	0.01
Half-Sibling	9	1.2	-0.24 ***	68	2.7	-0.04 ***
	SupTestR:SupTestR			SupTestR:SupTestR2		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	66	14.2	0.21	19	1.6	0.17 ***
Parent:Offspring	331	57.1	0.09	74	1.2	-0.26 ***
Sibling	127	21.5	0.44 *	31	2.3	-.28 ***
Half-Sibling	103	44	0.13	35	12.2	-0.01
	SupTestR:SupTestR3			SupTestR:SupTestR4		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	29	2.6	-0.03 ***	25	2.6	0.33 ***
Parent:Offspring	81	1.2	-0.09 ***	48	1.2	-0.19 ***
Sibling	32	5.7		22	1.9	-0.05 ***
Half-Sibling	29	8.8	-0.31	16	5	-0.51
	SupTestR2:TestR			SupTestR2:SupTestR		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	25	1	0.15 ***	25	2.1	0.05 ***
Parent:Offspring	55	5.8	-0.04	97	5.1	0.01
Sibling	26	1	0.19 ***^	31	2.3	-.28 ***
Half-Sibling	22	1.2	-0.11 ***	35	12.2	-0.01
	SupTestR2:SupTestR2			SupTestR2:SupTestR3		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	11	1.3	0.13 ***	14	1.5	0.17 ***
Parent:Offspring	33	1	0.02 ***^	26	1	-0.01 ***^
Sibling	20	1	0.25 ***^	11	1	0.16 ***^
Half-Sibling	13	1.8	-0.17	12	1	0.21 ***
	SupTestR2:SupTestR4			SupTestR3:TestR		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	9	1.2	0.69 ***	26	1	0.11 ***
Parent:Offspring	19	1	-0.08 ***^	94	4.9	-0.03
Sibling	8	1	0.13 ***^	25	8.3	-0.06
Half-Sibling	6	1	-0.26 ***^	17	1.3	-0.18 ***
	SupTestR3:SupTestR			SupTestR3:SupTestR2		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	27	3.2	0.64	7	1.2	0.34 ***
Parent:Offspring	149	12.2	0.03	38	1	0.26 ***^
Sibling	31	2.3	-.28 ***	11	1	0.16 ***^

Half-Sibling	29	8.8	-0.31	12	1	0.21 ***
	SupTestR3:SupTestR3			SupTestR3:SupTestR4		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	16	1.7	0.18 ***	13	1.6	0.52 ***
Parent:Offspring	43	1.1	-0.03 ***	30	1.1	-0.17 ***
Sibling	7	1	0.10 ***^	8	1	-0.07 ***^
Half-Sibling	9	1	0.36 ***^	4	1	0.03 ***^
	SupTestR4:TestR			SupTestR4:SupTestR		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	24	1	-0.08 ***	23	2.5	0.51 ***
Parent:Offspring	73	1	-0.21 ***	113	7.9	0.05
Sibling	15	1	-0.07 ***	22	1.9	-0.05 ***
Half-Sibling	9	1.2	-0.24 ***	16	5	-0.51
	SupTestR4:SupTestR2			SupTestR4:SupTestR3		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	7	1.2	0.31 ***	14	1.9	0.55 ***
Parent:Offspring	25	1	-0.01 ***^	38	1	0.26 ***^
Sibling	8	1	0.13 ***^	8	1	-0.07 ***^
Half-Sibling	6	1	-0.26 ***^	4	1	0.23 ***^
	SupTestR4:SupTestR4					
	count	equiv count	correlation			
Mother:Father	13	1.5	0.27 ***			
Parent:Offspring	25	1	0.13			
Sibling	5	1	-0.29 ***			
Half-Sibling	4	1	-0.09 ***^			

*** 0.01 ≤ p ≤ 0.05**
**** 0.001 ≤ p ≤ 0.009**
***** p ≤ 0.0009**
^ p ≥ 10.0
Standard error range for correlation values included in table: 0.0302 – ≥ 10.0

	TungRes:TungRes			TungRes:Btest03		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	359	338.8	0.44 ***	337	299.7	-0.04
Parent:Offspring	1855	954.8	0.34 ***	1019	231.1	-0.06
Sibling	776	392.7	0.39 ***	470	140.2	0.001
Half-Sibling	248	148	0.28 ***	149	86	0.05
	TungRes:Btest14			TungRes:Btest19		

	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	337	300.9	-0.01	346	312.7	-0.06
Parent:Offspring	1019	245.1	-0.07	1021	232.2	-0.06
Sibling	469	152	-0.01	471	144.2	0.03
Half-Sibling	149	87.2	0.05	147	82	0.05
	TungRes:Btest30			Btest03:TungRes		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	346	323.2	-0.07	353	305.4	0.09
Parent:Offspring	1022	267	-0.05	1774	1003.3	0.02
Sibling	472	191.4	0.03	470	140.2	0.001
Half-Sibling	147	89	0.08	149	86	0.05
	Btest03:Btest03			Btest03:Btest14		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	335	304.7	0.07	335	304.6	0.07
Parent:Offspring	970	397.3	0.10 *	970	395.9	0.09
Sibling	357	142.9	0.37 ***	356	145.6	0.36 ***
Half-Sibling	91	21.4	0.31	91	22.9	0.31
	Btest03:Btest19			Btest03:Btest30		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	344	311.5	0.13 *	344	313.4	0.07
Parent:Offspring	971	392.4	0.08	972	413.9	0.09
Sibling	358	151.5	0.38 ***	358	158.6	0.32 ***
Half-Sibling	89	21.2	0.31	89	25	0.28
	Btest14:TungRes			Btest14:Btest03		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	353	309.3	0.06	335	305.8	0.07
Parent:Offspring	1772	992.2	0.02	969	417.6	0.12 *
Sibling	469	152	-0.01	356	145.6	0.36 ***
Half-Sibling	149	87.2	0.05	91	22.9	0.31
	Btest14:Btest14			Btest14:Btest19		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	335	305.7	0.06	344	312.9	0.12 *
Parent:Offspring	969	418.5	0.12 *	970	414.1	0.12 *
Sibling	355	142.9	0.37 ***	357	147.3	0.37 ***
Half-Sibling	91	21.8	0.3	89	21.8	0.3
	Btest14:Btest30			Btest19:TungRes		
	count	equiv count	correlation	count	equiv count	correlation

Mother:Father	344	314.5	0.06	359	328	0.03
Parent:Offspring	971	438	0.14 **	1821	998	0.03
Sibling	357	154.2	0.31 ***	471	144.2	0.03
Half-Sibling	89	25.7	0.27	147	82	0.05
	Btest19:Btest03			Btest19:Btest14		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	341	317.4	0.09	341	317.2	0.09
Parent:Offspring	1006	398.2	0.1	1006	410.2	0.09
Sibling	358	151.5	0.38 ***	357	147.3	0.37 ***
Half-Sibling	89	21.2	0.31	89	21.8	0.3
	Btest19:Btest19			Btest19:Btest30		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	350	325	0.16 **	350	326.3	0.1
Parent:Offspring	1008	397	0.09	1009	419.2	0.10 *
Sibling	359	126.5	0.38 ***	359	136.7	0.32 ***
Half-Sibling	88	17.1	0.3	88	20.6	0.27
	Btest30:TungRes			Btest30:Btest03		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	359	331.7	0.03	341	319.9	0.08
Parent:Offspring	1821	1049.7	0.05	1006	393.1	0.09
Sibling	472	191.4	0.03	358	158.6	0.32 ***
Half-Sibling	147	89	0.08	89	25	0.28
	Btest30:Btest14			Btest30:Btest19		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	341	319.8	0.08	350	327.1	0.14 *
Parent:Offspring	1006	405.8	0.11 *	1008	390.8	0.10 *
Sibling	357	154.2	0.31 ***	359	136.7	0.32 ***
Half-Sibling	89	25.7	0.27	88	20.6	0.27
	Btest30:Btest30					
	count	equiv count	correlation			
Mother:Father	350	329	0.08			
Parent:Offspring	1009	412.6	0.11 *			
Sibling	359	128.9	0.27 **			
Half-Sibling	88	21.7	0.25			

*** $0.01 \leq p \leq 0.05$**
**** $0.001 \leq p \leq 0.009$**
***** $p \leq 0.0009$**
Standard error range for correlation values included in table: 0.0286 – 0.2301

	permgenDMFS:permgenDMFS			pergenDMFS:permgenDMFT		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	227	226.5	0.27 ***	228	227.4	0.23 ***
Parent:Offspring	795	370.8	0.25 ***	795	621.3	0.32 ***
Sibling	311	121.7	0.19 *	311	236.9	0.24 ***
Half-sibling	57	25.2	0.38	57	52.6	0.22
	permgeDMFS:permconseverDMFS			pergenDMFS:permconservDMFT		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	228	227.5	0.11	228	232.1	0.08
Parent:Offspring	795	300.4	0.31 ***	795	317.3	0.30 ***
Sibling	311	153.7	0.20 *	311	165	0.23 **
Half-sibling	57	34.9	0.14	57	35.4	0.08
	permgenDMFT:permgenDMFS			permgenDMFT:permgenDMFT		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	227	227.6	0.21 **	228	228.1	0.16 *
Parent:Offspring	795	355.9	0.23 ***	795	598.6	0.28 ***
Sibling	311	236.9	0.24 ***	311	263.8	0.36 ***
Half-sibling	57	52.6	0.22	57	67.6	0.11
	permgenDMFT:permconservDMFS			permgenDMFT:permconservDMFT		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	228	228.3	0.1	228	233.2	0.04
Parent:Offspring	795	295.6	0.24 ***	795	311	0.25 ***
Sibling	311	259.5	0.36 ***	311	253.3	0.38 ***
Half-sibling	57	55.2	0.04	57	53	0.01
	permconservDMFS:permgenDMFS			permconservDMFS:permgenDMFT		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	227	225.6	0.13 *	228	227.7	0.1
Parent:Offspring	795	367	0.08	795	619.4	0.12 **
Sibling	311	153.7	0.20 *	311	259.5	0.36 ***
Half-sibling	57	34.9	0.14	57	55.2	0.04
	permconservDMFS:permconservDMFS			permconservDMFS:permconservDMFT		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	228	227.1	0.16 *	228	232.2	0.1
Parent:Offspring	795	308.1	0.1	795	325.5	0.12 *
Sibling	311	129.2	0.42 ***	311	143.6	0.43 ***
Half-sibling	57	26.3	-0.04	57	28.3	-0.04
	permconservDMFT:permgenDMFS			permconservDMFT:permgenDMFT		
	count	equiv count	correlation	count	equiv count	correlation

Mother:Father	227	231.6	0.08	228	234.1	0.05
Parent:Offspring	795	377.3	0.07	795	635.5	0.09 *
Sibling	311	165	0.023 **	311	253.3	0.38 ***
Half-sibling	57	35.4	0.08	57	53	0.01
	permconserveDMFT:permconservDMFS			permconservDMFT:permconservDMFT		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	228	233.1	0.1	228	236.3	0.03
Parent:Offspring	795	318.2	0.05	795	333.1	0.07
Sibling	311	143.6	0.43 ***	311	132.6	0.44 ***
Half-sibling	57	28.3	-0.04	57	25.8	-0.04

*** 0.01 ≤ p ≤ 0.05**
**** 0.001 ≤ p ≤ 0.009**
***** p ≤ 0.0009**
Standard error range for correlation values included in table: 0.0362 – 0.2006

	BL03:BL03			BL03:BL14		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	370	369	0.15 **	370	370.1	0.16 **
Parent:Offspring	1082	776.3	0.15 ***	1082	767.3	0.15 ***
Sibling	387	262.8	0.24 ***	387	271.9	0.25 ***
Half-Sibling	93	74.7	0.26 *	93	77.9	0.25 *
	BL03:BL19			BL03:BL30		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	370	364.9	0.2 ***	370	368.5	0.17 ***
Parent:Offspring	1082	809.3	0.14 ***	1082	328.7	0.16 ***
Sibling	387	309.2	0.22 ***	387	319.9	0.20 ***
Half-Sibling	93	87.8	0.2	93	90.1	0.25 *
	BL14:BL03			BL14:BL14		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	370	367.8	0.18 ***	370	369.1	0.19 ***
Parent:Offspring	1082	760.1	0.16 ***	1082	751	0.16 ***
Sibling	387	271.9	0.25 ***	387	257.6	0.26 ***
Half-Sibling	93	77.9	0.25 *	93	73.8	0.25 *
	BL14:BL19			BL14:BL30		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	370	358.9	0.26 ***	370	364.5	0.23 ***
Parent:Offspring	1082	791.8	0.15 ***	1082	811.1	0.17 ***
Sibling	387	311.7	0.21 ***	387	322.7	0.19 ***
Half-Sibling	93	88.8	0.2	93	91.1	0.25 *

	BL19:BL03			BL19:BL14		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	370	371.9	0.15 **	370	375	0.16 **
Parent:Offspring	1082	748.5	0.16 ***	1082	739	0.17 ***
Sibling	387	309.2	0.22 ***	387	311.7	0.21 ***
Half-Sibling	93	87.8	0.2	93	88.8	0.2
	BL19:BL19			BL19:BL30		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	370	369	0.22 ***	370	372.5	0.18 ***
Parent:Offspring	1082	782.9	0.18 ***	1082	802.8	0.20 ***
Sibling	387	275.4	0.21 ***	387	299.5	0.19 **
Half-Sibling	93	76.5	0.15	93	82.8	0.2
	BL30:BL03			BL30:BL14		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	370	369.3	0.16 **	370	372.5	0.17 ***
Parent:Offspring	1082	758.9	0.18 ***	1082	749.4	0.18 ***
Sibling	387	319.9	0.20 ***	387	322.7	0.19 ***
Half-Sibling	93	90.1	0.25 *	93	91.1	0.25 *
	BL30:BL19			BL30:BL30		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	370	364.4	0.24 ***	370	368.9	0.20 ***
Parent:Offspring	1082	794.6	0.19 ***	1082	814.4	022 ***
Sibling	387	299.5	0.19 **	387	291.2	0.17 **
Half-Sibling	93	82.8	0.2	93	79.4	0.25 *

*** $0.01 \leq p \leq 0.05$**
**** $0.001 \leq p \leq 0.009$**
***** $p \leq 0.0009$**
Standard error range for correlation values included in table: 0.0334 – 0.1126

	PSR03:PSR03			PSR03:PSR14		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	370	369	0.16 **	370	370.8	0.17 **
Parent:Offspring	1082	767.2	0.16 ***	1082	779.3	0.16 ***
Sibling	387	260.6	0.25 ***	387	268.4	0.24 ***
Half-Sibling	93	74.4	0.26 *	93	76.3	0.24 *
	PSR03:PSR19			PSR03:PSR30		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	370	364.2	0.23 ***	370	366.9	0.19 ***
Parent:Offspring	1082	794.7	0.16 ***	1082	809.9	0.15 ***

Sibling	387	2998.2	0.23 ***	387	305.5	0.22 ***
Half-Sibling	93	85	0.24 *	93	86.5	0.24 *
	PSR14:PSR03			PSR14:PSR14		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	370	367	0.20 ***	370	369.1	0.20 ***
Parent:Offspring	1082	749.4	0.16 ***	1082	761.1	0.16 ***
Sibling	387	268.4	0.24 ***	387	265.1	0.24 ***
Half-Sibling	93	76.3	0.24 *	93	74.9	0.22
	PSR14:PSR19			PSR14:PSR30		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	370	363.5	0.24 ***	370	366.4	0.21 ***
Parent:Offspring	1082	774.8	0.16 ***	1082	789.7	0.14 ***
Sibling	387	305.5	0.23 ***	387	314.4	0.21 ***
Half-Sibling	93	86.7	0.22 *	93	88.7	0.22 *
	PSR19:PSR03			PSR19:PSR14		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	370	372.6	0.17 ***	370	373.2	0.18 ***
Parent:Offspring	1082	737.8	0.16 ***	1082	748.2	0.16 ***
Sibling	387	2998.2	0.23 ***	387	305.5	0.23 ***
Half-Sibling	93	85	0.24 *	93	86.7	0.22 *
	PSR19:PSR19			PSR19:PSR30		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	370	369.1	0.24 ***	370	371.1	0.21 ***
Parent:Offspring	1082	762.9	0.18 ***	1082	778.4	0.17 ***
Sibling	387	271.2	0.22 ***	387	288.2	0.20 ***
Half-Sibling	93	75.9	0.22	93	80.3	0.22
	PSR30:PSR03			PSR30:PSR14		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	370	370.7	0.17 **	370	371.1	0.17 ***
Parent:Offspring	1082	753	0.17 ***	1082	763.6	0.17 ***
Sibling	387	305.5	0.22 ***	387	314.4	0.21 ***
Half-Sibling	93	86.5	0.24 *	93	88.7	0.22 *
	PSR30:PSR19			PSR30:PSR30		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	370	366.6	0.23 ***	370	368.9	0.20 ***
Parent:Offspring	1082	779.4	0.19 ***	1082	795	0.18 ***
Sibling	387	288.2	0.20 ***	387	280.4	0.19 **
Half-Sibling	93	80.3	0.22	93	77.4	0.22

*** 0.01 ≤ p ≤ 0.05**

**** 0.001 ≤ p ≤ 0.009**
***** p ≤ 0.0009**
Standard error range for correlation values included in table: 0.0343 – 0.1111

	REC03:REC03			REC03:REC14		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	370	369	0.16 **	370	370.9	0.17 **
Parent:Offspring	1082	753.4	0.16 ***	1082	766.5	0.19 ***
Sibling	387	250.7	0.28 ***	387	260.8	0.27 ***
Half-Sibling	93	72.5	0.26 *	93	75.2	0.26 *
	REC03:REC19			REC03:REC30		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	370	365.1	0.22 ***	370	368.4	0.18 ***
Parent:Offspring	1082	794.4	0.15 ***	1082	810.9	0.15 ***
Sibling	387	290.4	0.26 ***	387	300.4	0.24 ***
Half-Sibling	93	83.4	0.2	93	85.8	0.24 *
	REC14:REC03			REC14:REC14		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	370	366.8	0.20 ***	370	369.1	0.20 ***
Parent:Offspring	1082	736.8	0.16 ***	1082	749.9	0.17 ***
Sibling	387	260.8	0.27 ***	387	257.1	0.26 ***
Half-Sibling	93	75.2	0.26 *	93	73.7	0.26 *
	REC14:REC19			REC14:REC30		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	370	361	0.26 ***	370	365.6	0.22 ***
Parent:Offspring	1082	777	0.15 ***	1082	793.4	0.16 ***
Sibling	387	297.8	0.25 ***	387	309.5	0.23 ***
Half-Sibling	93	85.4	0.2	93	88.1	0.24 *
	REC19:REC03			REC19:REC14		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	370	372.1	0.17 ***	370	374.5	0.18 ***
Parent:Offspring	1082	722.6	0.16 ***	1082	735.3	0.18 ***
Sibling	387	290.4	0.26 ***	387	297.8	0.25 ***
Half-Sibling	93	83.4	0.2	93	85.4	0.2
	REC19:REC19			REC19:REC30		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	370	369.1	0.23 ***	370	371.8	0.19 ***
Parent:Offspring	1082	764.4	0.17 ***	1082	780.7	0.18 ***
Sibling	387	267.1	0.23 ***	387	285	0.21 ***

Half-Sibling	93	75	0.15	93	79.7	0.18
	REC30:REC03			REC30:REC14		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	370	369.5	0.17 ***	370	371.8	0.18 ***
Parent:Offspring	1082	740	0.17 ***	1082	753	0.19 ***
Sibling	387	300.4	0.24 ***	387	309.5	0.23 ***
Half-Sibling	93	85.8	0.24 *	93	88.1	0.24 *
	REC30:REC19			REC30:REC30		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	370	365.5	0.23 ***	370	368.9	0.19 ***
Parent:Offspring	1082	782.6	0.18 ***	1082	799.3	0.19 ***
Sibling	387	285	0.21 ***	387	278.7	0.20 ***
Half-Sibling	93	79.7	0.18	93	77.2	0.22

*** 0.01 ≤ p ≤ 0.05**
**** 0.001 ≤ p ≤ 0.009**
***** p ≤ 0.0009**
Standard error range for correlation values included in table: 0.0342 – 0.1136

	S1b:S1b			S1b:S2b		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	369	368.1	0.12 *	369	368.4	0.12 *
Parent:Offspring	67	58.8	0.01	67	61.2	0.04
Sibling	3	NE	1	3	6.5	0.71
Half-Sibling	NI	NI	NI	NI	NI	NI
	S1b:S3b			S1b:S4b		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	369	366.7	0.13 *	369	366.9	0.17 **
Parent:Offspring	67	61.1	0.05	67	60	-0.09
Sibling	3	6.5	0.71	3	7.5	0.71
Half-Sibling	NI	NI	NI	NI	NI	NI
	S1b:S5b			S1b:S6b		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	369	365.8	0.18 ***	369	379.2	0.15 **
Parent:Offspring	67	63.2	0.05	67	60.2	-0.09
Sibling	3	6.3	0.25	3	7.3	0.71
Half-Sibling	NI	NI	NI	NI	NI	NI
	S2b:S1b			S2b:S2b		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	369	367.8	0.13 *	369	368.1	0.13 *

Parent:Offspring	67	58.6	0.04	67	61	0.06
Sibling	3	6.5	0.71	3	3.8	0.33
Half-Sibling	NI	NI	NI	NI	NI	NI
	S2b:S3b			S2b:S4b		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	369	366.3	0.14 **	369	366.3	0.17 ***
Parent:Offspring	67	60.9	0.07	67	60.1	-0.08
Sibling	3	4.1	0.33	3	4.3	0.33
Half-Sibling	NI	NI	NI	NI	NI	NI
	S2b:S5b			S2b:S6b		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	369	365.2	0.19 ***	369	378.9	0.16 **
Parent:Offspring	67	62.5	0.07	67	60.2	-0.08
Sibling	3	NE	NE	3	4.3	0.33
Half-Sibling	NI	NI	NI	NI	NI	NI
	S3b:S1b			S3b:S2b		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	369	369.2	0.11 *	369	369.4	0.11 *
Parent:Offspring	67	68.2	0.02	67	60.6	0.05
Sibling	3	6.5	0.71	3	4.1	0.33
Half-Sibling	NI	NI	NI	NI	NI	NI
	S3b:S3b			S3b:S4b		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	369	368.1	0.14 **	369	367.2	0.15 **
Parent:Offspring	67	60.6	0.06	67	59.8	-0.09
Sibling	3	3.8	0.33	3	4.4	0.33
Half-Sibling	NI	NI	NI	NI	NI	NI
	S3b:S5b			S3b:S6b		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	369	366.4	0.17 **	369	379.3	0.14 **
Parent:Offspring	67	62.4	0.06	67	59.9	-0.08
Sibling	3	NE	NE	3	4.3	0.33
Half-Sibling	NI	NI	NI	NI	NI	NI
	S4b:S1b			S4b:S2b		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	369	369.3	0.15 **	369	369.7	0.15 **
Parent:Offspring	67	56	-0.03	67	58.2	-0.10
Sibling	3	7.5	0.71	3	4.3	0.33

Half-Sibling	NI	NI	NI	NI	NI	NI
	S4b:S3b			S4b:S4b		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	369	369	0.14 **	369	368.3	0.19 ***
Parent:Offspring	67	58.3	-0.09	67	54.3	-0.06
Sibling	3	4.4	0.33	3	3.8	0.33
Half-Sibling	NI	NI	NI	NI	NI	NI
	S4b:S5b			S4b:S6b		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	369	367.2	0.21 ***	369	379.3	0.17 ***
Parent:Offspring	67	58.4	-0.09	67	55.5	-0.06
Sibling	3	NE	NE	3	4	0.33
Half-Sibling	NI	NI	NI	NI	NI	NI
	S5b:S1b			S5b:S2b		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	369	370.1	0.15 **	369	370.5	0.15 **
Parent:Offspring	67	55.4	-0.04	67	57	-0.10
Sibling	3	6.3	0.25	3	NE	NE
Half-Sibling	NI	NI	NI	NI	NI	NI
	S5b:S3b			S5b:S4b		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	369	369.6	0.14 **	369	369.4	0.19 ***
Parent:Offspring	67	57.2	-0.09	67	55.4	-0.06
Sibling	3	NE	NE	3	NE	NE
Half-Sibling	NI	NI	NI	NI	NI	NI
	S5b:S5b			S5b:S6b		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	369	368.4	0.21 ***	369	380.2	0.18 ***
Parent:Offspring	67	58.6	-0.09	67	56.3	-0.06
Sibling	3	4.3	-0.50	3	NE	NE
Half-Sibling	NI	NI	NI	NI	NI	NI
	S6b:S1b			S6b:S2b		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	369	369.3	0.16 **	369	369.7	0.17 **
Parent:Offspring	67	58.5	-0.06	67	60.8	-0.11
Sibling	3	7.3	0.71	3	4.3	0.33
Half-Sibling	NI	NI	NI	NI	NI	NI
	S6b:S3b			S6b:S4b		

	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	369	369.1	0.15 **	369	369.4	0.19 ***
Parent:Offspring	67	60.9	-0.11	67	58.8	-0.07
Sibling	3	4.3	0.33	3	4	0.33
Half-Sibling	NI	NI	NI	NI	NI	NI
	S6b:S5b			S6b:S6b		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	369	368.4	0.20 ***	369	379.5	0.17 **
Parent:Offspring	67	62.7	-0.11	67	59.4	-0.07
Sibling	3	NE	NE	3	3.8	0.33
Half-Sibling	NI	NI	NI	NI	NI	NI

*** 0.01 ≤ p ≤ 0.05**
**** 0.001 ≤ p ≤ 0.009**
***** p ≤ 0.0009**
NE Value is not estimable
NI No results produced
Standard error range for correlation values included in table: 0.0498 – 0.5826

	S1:S1			S1:S2		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	369	68	0.05	369	368.6	0.03
Parent:Offspring	67	65.3	0.02	67	66.5	0.05
Sibling	3	3.5	-0.20	3	NE	NE
Half-Sibling	NI	NI	NI	NI	NI	NI
	S1:S3			S1:S4		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	369	368.7	0.05	369	368.4	0.08
Parent:Offspring	67	65.3	0.05	67	68.5	-0.08
Sibling	3	3.7	-0.20	3	6.4	-0.76
Half-Sibling	NI	NI	NI	NI	NI	NI
	S1:S5			S1:S6		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	369	368.9	0.07	369	378.7	0.05
Parent:Offspring	67	65.5	-0.08	67	67	-0.16
Sibling	3	3.8	0.11	3	4.3	-0.32
Half-Sibling	NI	NI	NI	NI	NI	NI
	S2:S1			S2:S2		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	369	365.9	0.09	369	368	0.04
Parent:Offspring	67	65.8	0.05	67	67	0.08

Sibling	3	NE	NE	3	4.3	-0.50
Half-Sibling	NI	NI	NI	NI	NI	NI
	S2:S3			S2:S4		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	369	367.1	0.09	369	365.6	0.12 *
Parent:Offspring	67	65.7	0.08	67	67.4	-0.07
Sibling	3	NE	NE	3	NE	NE
Half-Sibling	NI	NI	NI	NI	NI	NI
	S2:S5			S2:S6		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	369	367.9	0.08	369	377.9	0.07
Parent:Offspring	67	64.7	-0.07	67	66.2	-0.14
Sibling	3	3.3	0.3	3	2.8	0.43 ***
Half-Sibling	NI	NI	NI	NI	NI	NI
	S3:S1			S3:S2		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	369	366.8	0.09	369	368.6	0.07
Parent:Offspring	67	64	0.03	67	65.2	0.06
Sibling	3	3.7	-0.20	3	NE	NE
Half-Sibling	NI	NI	NI	NI	NI	NI
	S3:S3			S3:S4		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	369	368	0.09	369	368	0.1
Parent:Offspring	67	64	0.06	67	67.5	-0.07
Sibling	3	3.5	-0.20	3	6.5	-0.76
Half-Sibling	NI	NI	NI	NI	NI	NI
	S3:S5			S3:S6		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	369	368.7	0.09	369	378.5	0.07
Parent:Offspring	67	64.5	-0.08	67	66.2	-0.15
Sibling	3	3.8	0.11	3	4.4	-0.32
Half-Sibling	NI	NI	NI	NI	NI	NI
	S4:S1			S4:S2		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	369	367.6	0.09	369	369.4	0.07
Parent:Offspring	67	63.1	-0.004	67	62.8	-0.09
Sibling	3	6.4	-0.76	3	NE	NE
Half-Sibling	NI	NI	NI	NI	NI	NI

	S4:S3			S4:S4		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	369	368.1	0.1	369	368.2	0.15 **
Parent:Offspring	67	36.1	-0.09	67	64.6	-0.04
Sibling	3	6.5	-0.76	3	6.2	-0.76 *
Half-Sibling	NI	NI	NI	NI	NI	NI
	S4:S5			S4:S6		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	369	370.6	0.11 *	369	378.8	0.09
Parent:Offspring	67	60.7	-0.06	67	63.4	-0.10
Sibling	3	5	-0.65	3	5.9	-0.69
Half-Sibling	NI	NI	NI	NI	NI	NI
	S5:S1			S5:S2		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	369	366.8	0.11 *	369	368.2	0.08
Parent:Offspring	67	63.7	-0.01	67	63.4	-0.08
Sibling	3	3.8	0.11	3	3.3	0.3
Half-Sibling	NI	NI	NI	NI	NI	NI
	S5:S3			S5:S4		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	369	367.4	0.11 *	369	364.4	0.17 **
Parent:Offspring	67	63.8	-0.09	67	64	-0.04
Sibling	3	3.8	0.11	3	5	-0.65
Half-Sibling	NI	NI	NI	NI	NI	NI
	S5:S5			S5:S6		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	369	368.2	0.13 *	369	376.4	0.11 *
Parent:Offspring	67	60.1	-0.06	67	63	-0.11
Sibling	3	3.3	-0.06	3	4.2	-0.34
Half-Sibling	NI	NI	NI	NI	NI	NI
	S6:S1			S6:S2		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	369	369.4	0.08	369	370.3	0.05
Parent:Offspring	67	68.3	-0.04	67	68.5	-0.10
Sibling	3	4.3	-0.32	3	2.8	0.43 ***
Half-Sibling	NI	NI	NI	NI	NI	NI
	S6:S3			S6:S4		
	count	equiv count	correlation	count	equiv count	correlation

Mother:Father	369	369.8	0.08	369	369.7	0.11 *
Parent:Offspring	67	68.4	-0.10	67	69.9	-0.06
Sibling	3	4.4	-0.32	3	5.9	-0.69
Half-Sibling	NI	NI	NI	NI	NI	NI
	S6:S5			S6:S6		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	369	371.3	0.07	369	379.5	0.05
Parent:Offspring	67	66.2	-0.07	67	68.8	-0.13
Sibling	3	4.2	-0.34	3	4.3	-0.50
Half-Sibling	NI	NI	NI	NI	NI	NI

*** 0.01 ≤ p ≤ 0.05**
**** 0.001 ≤ p ≤ 0.009**
***** p ≤ 0.0009**
NE Value is not estimable
NI No results produced
Standard error range for correlation values included in table: 0.0509 – 0.7417

	S1r:S1r			S1r:S2r		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	369	368.1	0.13 *	369	369.1	0.12 *
Parent:Offspring	67	62.2	0.07	67	62	-0.01
Sibling	3	NE	NE	3	NE	NE
Half-Sibling	NI	NI	NI	NI	NI	NI
	S1r:S3r			S1r:S4r		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	369	366.6	0.15 **	369	367.5	0.14 **
Parent:Offspring	67	62	-0.01	67	61.3	-0.14
Sibling	3	NE	NE	3	NE	NE
Half-Sibling	NI	NI	NI	NI	NI	NI
	S1r:S5r			S1r:S6r		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	369	367.5	0.14 **	369	377.7	0.15 **
Parent:Offspring	67	62	-0.06	67	58	-0.13
Sibling	3	NE	NE	3	NE	NE
Half-Sibling	NI	NI	NI	NI	NI	NI
	S2r:S1r			S2r:S2r		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	369	367	0.14 **	369	368.1	0.14 **
Parent:Offspring	67	61.3	0.1	67	61.8	0.01
Sibling	3	NE	NE	3	NE	NE

Half-Sibling	NI	NI	NI	NI	NI	NI
	S2r:S3r			S2r:S4r		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	369	366.8	0.16 **	369	367.5	0.15 **
Parent:Offspring	67	61.8	0.01	67	62	-0.12
Sibling	3	NE	NE	3	NE	NE
Half-Sibling	NI	NI	NI	NI	NI	NI
	S2r:S5r			S2r:S6r		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	369	367.4	0.15 **	369	377.7	0.17 ***
Parent:Offspring	67	62	-0.04	67	58.6	-0.12
Sibling	3	NE	NE	3	NE	NE
Half-Sibling	NI	NI	NI	NI	NI	NI
	S3r:S1r			S3r:S2r		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	369	369.3	0.12 *	369	369.3	0.14 **
Parent:Offspring	67	60.9	0.08	67	61.2	-0.01
Sibling	3	NE	NE	3	NE	NE
Half-Sibling	NI	NI	NI	NI	NI	NI
	S3r:S3r			S3r:S4r		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	369	368.2	0.16 **	369	367.8	0.15 **
Parent:Offspring	67	61.2	-0.05	67	61.4	-0.13
Sibling	3	NE	NE	3	NE	NE
Half-Sibling	NI	NI	NI	NI	NI	NI
	S3r:S5r			S3r:S6r		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	369	367.4	0.16 **	369	379.2	0.15 **
Parent:Offspring	67	61.5	-0.05	67	58	-0.13
Sibling	3	NE	NE	3	NE	NE
Half-Sibling	NI	NI	NI	NI	NI	NI
	S4r:S1r			S4r:S2r		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	369	368.6	0.13 *	369	368.7	0.14 **
Parent:Offspring	67	61.3	0.02	67	61.8	-0.12
Sibling	3	NE	NE	3	NE	NE
Half-Sibling	NI	NI	NI	NI	NI	NI
	S4r:S3r			S4r:S4r		

	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	369	368.5	0.15 **	369	368.2	0.15 **
Parent:Offspring	67	61.8	-0.11	67	61.7	-0.10
Sibling	3	NE	NE	3	NE	NE
Half-Sibling	NI	NI	NI	NI	NI	NI
	S4r:S5r			S4r:S6r		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	369	368.4	0.15 **	369	376.9	0.17 **
Parent:Offspring	67	61.6	-0.14	67	58.2	-0.09
Sibling	3	NE	NE	3	NE	NE
Half-Sibling	NI	NI	NI	NI	NI	NI
	S5r:S1r			S5r:S2r		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	369	368.7	0.12 *	369	368.8	0.14 **
Parent:Offspring	67	61.5	0.01	67	61.3	-0.12
Sibling	3	NE	NE	3	NE	NE
Half-Sibling	NI	NI	NI	NI	NI	NI
	S5r:S3r			S5r:S4r		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	369	368.9	0.14 **	369	368.1	0.15 **
Parent:Offspring	67	61.4	-0.12	67	62	-0.10
Sibling	3	NE	NE	3	NE	NE
Half-Sibling	NI	NI	NI	NI	NI	NI
	S5r:S5r			S5r:S6r		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	369	368.3	0.15 **	369	376.8	0.17 **
Parent:Offspring	67	62	-0.14	67	58.5	-0.10
Sibling	3	NE	NE	3	NE	NE
Half-Sibling	NI	NI	NI	NI	NI	NI
	S6r:S1r			S6r:S2r		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	369	370.7	0.14 **	369	370.8	0.16 **
Parent:Offspring	67	63.1	-0.02	67	63.1	-0.14
Sibling	3	NE	NE	3	NE	NE
Half-Sibling	NI	NI	NI	NI	NI	NI
	S6r:S3r			S6r:S4r		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	369	369.3	0.16 **	369	371.5	0.14 **

Parent:Offspring	67	63.2	-0.14	67	63	-0.11
Sibling	3	NE	NE	3	NE	NE
Half-Sibling	NI	NI	NI	NI	NI	NI
	S6r:S5r			S6r:S6r		
	count	equiv count	correlation	count	equiv count	correlation
Mother:Father	369	371.6	0.14 **	369	379.5	0.16 **
Parent:Offspring	67	62.8	-0.16	67	59.4	-0.11
Sibling	3	NE	NE	3	NE	1
Half-Sibling	NI	NI	NI	NI	NI	NI

*** 0.01 ≤ p ≤ 0.05**
**** 0.001 ≤ p ≤ 0.009**
***** p ≤ 0.0009**
NE Value is not estimable
NI No results produced
Standard error range for correlation values included in table: 0.0501 – 0.1311

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