# The Association of Moderate/Severe Periodontitis (MSP), Pregnancy, and Two Single Nucleotide Polymorphisms (SNPs) in the Vitamin D Receptor (VDR) Gene: NHANES III, 1988-1994

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**CDC** Reproductive Health

## Background

- Pregnancy can exacerbate an existing periodontal condition
- Periodontal disease has been associated with a number of adverse reproductive outcomes
- Activation of inflammatory pathway implicated in adverse reproductive outcomes since oral microorganisms and cytokines have been identified in amniotic fluid

## Purpose

To identify candidate genes for adverse reproductive outcomes using periodontal conditions as a "surrogate" outcome

## Objectives

- What genes are associated with periodontal conditions in a population of reproductive aged women?
- Can pregnancy modify this association?

## Methods

**Data Sources: NHANES III Collaborative Genomics Project**

1. NHANES III (1988-1994)
   - National population-based weighted survey data (NCHS)
   - Over-sampling of youth, elderly, African-Americans, and Mexican-Americans
2. NHANES III DNA Data Bank (1991-1994)
   - Approximately 7,000 DNA samples >12 years of age
3. 2002 CDC Cross-CIO Collaborative Working Group

**Case/Control Study of Moderate/Severe Periodontitis (MSP)**

- Candidate gene association study
- Study population of women 17-54 years of age (n = 2,103)
- Case definition of periodontitis based on CDC definition of moderate/severe periodontitis (MSP)

## Analysis

- We used the log-additive model to identify genes associated with periodontitis among 13 genes/25 SNPs in the inflammatory metabolic pathways
- Multiple logistic regression was performed on significant associations using potential confounders as covariates
- Gene-environment interactions were included

## Results

### Table 1

Study population characteristics among Non-Hispanic white (NHW), Non-Hispanic black (NHB), and Mexican-Americans (MA) (n = 2,103) Sample sizes are unweighted

| Variable | NHW n=679 | % (SE) NHB n=763 | MA n=661 | p-value |
|---|---|---|---|---|
| Mean Age (y) | 34.7 (0.7) | 33.0 (0.4) | 32. 0 (0.4) | <0.001 |
| **Education (y)** | | | | |
| <12 | 12.4 (1.4) | 22.7 (2.2) | 54.2 (4.0) | |
| 12 | 35.1 (2.2) | 42.4 (2.6) | 30.3 (3.0) | |
| >12 | 52.5 (2.7) | 34.9 (2.9) | 15.6 (2.3) | 0.10 |
| **Tobacco Use** | | | | |
| Never smoker | 53.9 (2.6) | 66.0 (2.5) | 75.2 (1.9) | 0.02 |
| Former smoker | 18.9 (1.7) | 7.6 (1.0) | 13.0 (1.3) | |
| Current smoker | 27.2 (2.2) | 26.4 (2.0) | 11.8 (1.4) | |
| **Dental visit in the last 12 months** | | | | |
| Yes | 60.0 (2.8) | 46.9 (2.3) | 36.1 (2.4) | 0.01 |
| No | 40.0 (2.8) | 53.1 (2.3) | 63.9 (2.4) | |
| **Poverty Income Ratio** | | | | |
| <100 | 8.3 (1.8) | 36.6 (3.5) | 37.1 (3.2) | |
| 100-199 | 18.2 (2.4) | 26.8 (2.2) | 33.6 (2.8) | |
| >200 | 73.5 (3.0) | 36.6 (3.2) | 29.3 (1.5) | 0.06 |
| **Diabetes** | | | | |
| Yes | 2.7 (0.8) | 4.4 (0.9) | 6.6 (1.2) | |
| No | 97.3 (0.8) | 95.6 (0.9) | 93.4 (1.2) | 0.64 |
| **Reproductive History** | | | | |
| Never been pregnant | 25.8 (2.3) | 16.2 (1.6) | 15.8 (2.6) | <0.001 |
| Ever been pregnant | 74.2 (2.3) | 83.8 (1.6) | 84.2 (2.6) | |

### Table 2

Prevalence of MSP and characteristics of the population with MSP by race/ethnicity (n= 94)

| Variable | NHW | % (SE) NHB | MA | p-value |
|---|---|---|---|---|
| **Prevalence** | 2.5 (0.7) | 6.1 (1.1) | 3.5 (0.6) | 0.05 |
| **Mean Age (y)** | 44.5 (1.3) | 37.6 (1.3) | 44.7 (1.6) | <0.001 |
| **Education (y)** | | | | |
| <12 | 22.5 (10.0) | 38.2 (9.6) | 78.2 (9.4) | 0.14 |
| 12 | 35.5 (11.3) | 32.2 (9.6) | 18.4 (8.0) | |
| >12 | 41.9 (14.1) | 29.1 (8.9) | 3.4 (2.6) | |
| **Tobacco Use** | | | | |
| Never smoker | 14.8 (9.4) | 53.7 (9.8) | 64.3 (9.7) | 0.008 |
| Former smoker | 26.2 (14.3) | 3.9 (2.6) | 10.5 (8.1) | |
| Current smoker | 59.1 (16.5) | 42.4 (10.1) | 25.2 (9.1) | |
| **Dental visit in the last 12 months** | | | | |
| Yes | 25 (12.5) | 47.5 (8.4) | 26.8 (10.3) | 0.02 |
| No | 75 (12.5) | 52.5 (8.4) | 73.2 (10.3) | |
| **Poverty Income Ratio** | | | | |
| <100 | 27.6 (12.5) | 27.7 (6.7) | 53.5 (9.8) | |
| 100-199 | 24.4 (11.6) | 36.9 (7.4) | 28.9 (6.4) | |
| >200 | 48.0 (14.8) | 36.5 (7.7) | 17.6 (8.7) | 0.2 |
| **Diabetes** | | | | |
| Yes | 0 (0) | 8.5 (4.6) | 19.2 (8.0) | 0.7 |
| No | 100 (0) | 91.5 (4.6) | 80.8 (8.0) | |
| **Reproductive History** | | | | |
| Never been pregnant | 0 (0) | 12.1 (4.6) | 3.9 (3.0) | 0.001 |
| Ever been pregnant | 100 (0) | 87.9 (4.6) | 96.1 (3.0) | |

### Table 3

Genes/SNPs in the inflammatory/metabolic pathways associated with MSP (unadjusted)

| Gene | p-Value | Gene | p-Value | Gene | p-Value |
|---|---|---|---|---|---|
| CCR2 | 0.99 | IL4R-05 | 0.58 | **MGC4093-03** | **0.03** |
| CRP-B | 0.12 | -06 | 0.43 | MGC4093-01 | 0.38 |
| CRP-C | 0.45 | IL10-014 | 0.20 | TNF-01 | 0.09 |
| FCGR2A | 0.57 | -02 | 0.21 | -04 | 0.32 |
| IL1B-09 | 0.53 | -03 | 0.30 | **-02** | **0.05** |
| IL4 -01 | 0.90 | **MBL2 -11** | **0.02** | MTHFR-01 | 0.57 |
| -17 | 0.72 | -12 | 0.74 | -02 | 0.82 |
| -02 | 0.54 | TGFB1-01 | 0.16 | **VDR-01** | **0.009** |
| | | | | **-07** | **0.003** |

### Table 4

Allele frequencies of Vitamin D Receptor (VDR) SNP rs731236; C<T and rs2239185; C<T by case/control status (cases = with MSP, controls = no MSP) among NHW, NHB, and MA.

| VDR SNP rs731236 | | | | | | |
|---|---|---|---|---|---|---|
| | **NHW** | | **NHB** | | **MA** | |
| | Cases | Controls | Cases | Controls | Cases | Controls |
| C | 61% | 39% | 35% | 28% | 34% | 24% |
| T | 39% | 61% | 65% | 72% | 67% | 76% |

| VDR SNP rs2239185 | | | | | | |
|---|---|---|---|---|---|---|
| | **NHW** | | **NHB** | | **MA** | |
| | Cases | Controls | Cases | Controls | Cases | Controls |
| C | 19% | 349% | 41.5% | 42% | 56% | 58% |
| T | 81% | 51% | 58.5% | 58% | 44% | 42% |

### Table 5

VDR SNP associations with MSP stratified by reproductive history and race/ethnicity (unadjusted)

| VDR SNPs | rs731236 unadjusted OR (95% CI) | rs2239185 unadjusted OR (95% CI) |
|---|---|---|
| **Reproductive History** | | |
| Never been pregnant | 0.5 (0.2-1.1) | **0.5 (0.3-0.8)** |
| Ever been pregnant | **1.9 (1.2-2.9)** | **0.3 (0.1-0.8)** |
| **Race/ethnicity** | | |
| NHW | **2.3 (1.2-4.5)** | **0.3 (0.1-0.8)** |
| NHB | 1.4 (0.9-2.2) | 1.0 (0.6-1.5) |
| MA | 1.6 (0.9-3.1) | 0.9 (0.6-1.6) |

### Table 6

VDR SNP associations with MSP (adjusted)

| VDR SNPs | rs731236 adjusted OR (95% CI) | rs2239185 adjusted OR (95% CI) |
|---|---|---|
| Mean Age (y) | **1.1 (1.1 – 1.2)** | **1.1 (1.1 – 1.2)** |
| **Race/ethnicity** | | |
| NHW | REF | REF |
| NHB | 4.3 (0.7 – 28.3) | 0.2 (0.03 – 1.3) |
| MA | 2.9 (0.3 – 27.0) | 0.06 (0.01 – 0.7) |
| **Tobacco Use** | | |
| Never smoker | REF | REF |
| Former smoker | 1.8 (0.6 – 6.0) | 2.2 (0.6 – 8.4) |
| Current smoker | **4.1 (1.2 – 14.2)** | **4.6 (1.2 – 17.0)** |
| **Reproductive History** | | |
| Never been pregnant | REF | REF |
| Ever been pregnant | 0.1 (0.01 – 1.3) | 1.6 (0.1 – 22.5) |
| **VDR** | 0.5 (0.2 – 1.4) | **0.2 (0.1 – 0.6)** |
| **VDR* Reproductive History** | | |
| Never been pregnant | REF | REF |
| Ever been pregnant | **5.7 (1.6 – 20.5)** | 1.2 (0.3 – 5.4) |
| **VDR* Race/ethnicity** | | |
| NHW | REF | REF |
| NHB | 0.8 (0.3 – 1.7) | **3.4 (1.1 – 10.4)** |
| MA | 0.6 (0.2 – 2.0) | **4.8 (1.3 – 17.1)** |

* Adjusted for education, number of dental visits, poverty income ratio, & diabetes status

## Summary and Limitations

### Summary

- Identified two SNPs in the VDR gene to be associated with MSP
- Women who were ever pregnant and who had MSP were more likely to be carriers of rs731236 compared to non-pregnant women
- Non-Hispanic black women and Mexican American women were more likely to carry VDR SNP rs2239185 compared to non-Hispanic white women

### Study limitations

- Small number of MSP cases in each race/ethnicity category
- All non-Hispanic white women who had MSP also had a past pregnancy