Gene Variants as Risk Factors for Gastroschisis

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In a population-based case-control study in California of 228 infants, we investigated 75 genetic variants in 20 genes and risk of gastroschisis with regard to maternal age, race/ethnicity, vitamin use, and smoking exposure. We hypothesized that genes related to vascular compromise may interact with environmental factors to affect the risk of gastroschisis. Haplotypes were constructed for 75 gene variants using the HaploView program. Risk for gastroschisis associated with each gene variant was calculated for both the homozygotes and the heterozygotes, with the homozygous wildtypes as the referent. Risks were estimated as odds ratios (ORs) with 95% confidence intervals (CIs) by logistic regression.

There have been four studies of gene variants and gastroschisis over the past 10 years [Cardonick et al., 2005; Torfs et al., 2006; Feldkamp et al., 2012; Jenkins et al., 2014]. One investigated polymorphisms in 32 genes (representing enzymes involved in angiogenesis, blood vessel integrity, inflammation, wound repair, and dermal or epidermal strength) in a case-control study of 57 cases of gastroschisis and 506 controls [Torfs et al., 2006]. This study found that gene variants that have been implicated with gastroschisis frequency have been inexplicably increasing around the world for several decades [Castilla et al., 2008]. Several studies of familial cases of gastroschisis have suggested an underlying genetic susceptibility for gastroschisis [Torfs et al., 1996; Kohl et al., 2010; Feldkamp et al., 2011]. However, given the recent increase in frequency, it is not likely that genetic variants are solely responsible for the occurrence of gastroschisis. We hypothesize that gene variants in conjunction with additional exposures or covariates may increase the risk of gastroschisis.

Gastroschisis frequency has been inexplicably increasing around the world for several decades [Castilla et al., 2008]. Several studies of familial cases of gastroschisis have suggested an underlying genetic susceptibility for gastroschisis [Torfs et al., 1996; Kohl et al., 2010; Feldkamp et al., 2011]. However, given the recent increase in frequency, it is not likely that genetic variants are solely responsible for the occurrence of gastroschisis. We hypothesize that gene variants in conjunction with additional exposures or covariates may increase the risk of gastroschisis.

INTRODUCTION

Gastroschisis is an abdominal wall defect that is present at birth where a portion of the intestines protrudes outside of the body. The defect most likely occurs between the 5th and 8th week gestation and the pathogenesis is largely unknown. This congenital anomaly affects approximately 4.5 infants per 10,000 U.S. live births [Parker et al., 2010]. The most consistently observed risk factor is maternal age of <20 years [Rasmussen and Frias, 2008; Vu et al., 2008].

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blood pressure regulation and cell–cell interaction were associated with an increased risk for a gastroschisis for heterozygotes–[Torfs et al., 2006]. Some variants showed a strong interaction with maternal smoking, which supports the hypothesis of a vascular compromise as part of a multifactorial etiology of gastroschisis involving both genes and environmental factors [Torfs et al., 2006]. A second study found no association between variants in MTHFR, a gene related to homocysteine metabolism, and gastroschisis in 31 cases and 52 controls [Cardonick et al., 2005]. An additional study found no association between gastroschisis and AEBP1 variants, a gene that encodes an intracellular protein involved in pro-inflammatory processes [Feldkamp et al., 2012]. The fourth study did not find consistent associations between variants of three genes that code for enzymes involved in metabolism of some cigarette smoke constituents, CYP1A1, CYP1A2, and NAT2, nor effect modification with maternal smoking, and risk of gastroschisis [Jenkins et al., 2014].

To extend this relatively small body of work, in a population-based case-control study, we investigated 75 genetic variants in 20 genes and risk of gastroschisis with regard to maternal age, race/ethnicity, vitamin use, and smoking exposure. Many of these genes and variants were also examined in the previous study by Torfs et al. [2006], but this study includes different cases and controls than those investigated in that study. We hypothesized that genes related to vascular compromise may interact with these factors to affect the risk of gastroschisis. For this reason, we chose genes with the following patho-genetic groupings: homocysteine metabolism, blood pressure regulation, coagulation, cell–cell interaction, and inflammatory response.

METHODS

Study Population

The California Center of the National Birth Defects Prevention Study [Yoon et al., 2001; Reefhuis et al., 2015] is a collaborative partnership between Stanford University and the California Birth Defects Monitoring Program in the Department of Public Health. Since 1997, the Center has been collecting data from women whose residence at the time of delivery was in one of eight counties in the San Joaquin Valley. The California Birth Defects Monitoring Program is a surveillance program that is population-based [Croen et al., 1991].

To identify cases with birth defects, data collection staff visit all hospitals with obstetric or pediatric services, cytogenetic laboratories, and all clinical genetics prenatal and postnatal outpatient services. Cases included infants or fetuses with gastroschisis confirmed by clinical geneticists based on clinical, surgical, or autopsy reports. Cases recognized or strongly suspected to have single-gene conditions or chromosomal abnormalities or with identifiable syndromes were ineligible [Rasmussen et al., 2003], given their presumed distinct underlying etiology. Controls included non-malformed live-born infants randomly selected from birth hospitals to represent the population from which the cases were selected. The current analysis included 79 gastroschisis cases and 149 controls with estimated dates of delivery from October 1, 1997, to December 31, 2001 in the California Center of the National Birth Defects Prevention Study.

Maternal interviews were conducted using a standardized, computer-based questionnaire, by telephone, in English or Spanish, between six weeks and 24 months after the infant’s estimated date of delivery. Interviews were conducted with mothers of 80% of eligible cases (n = 63) and 71% of controls (n = 106).

Genotyping

Prior to leaving the hospital, a few drops of blood from the newborn’s heel are collected on filter paper as part of the California newborn screening program. Genomic DNA was extracted from infant dried bloodspots using MasterPure™ Complete DNA and RNA Purification Kit (Epicenter Biotechnologies Madison, WI) and 10 ng genomic DNA was then used for whole genome amplification (WGA) using Qiagen’s (Repli-g™) amplification kit, which utilizes a technique called Multiple Displacement Amplification. This provides unbiased and accurate amplification of whole genomes.

For SNP genotyping, multiplexed genotyping assays were developed utilizing a high throughput platform, the Sequenom MALDI-TOF Mass Array System. This protocol requires 5–10 ng of WGA DNA. The assay consists of an initial locus-specific PCR reaction, followed by single base extension using mass-modified dideoxynucleotide terminators of an oligonucleotide primer which anneals immediately upstream of the polymorphic site of interest. Using MALDI-TOF mass spectrometry, the distinct mass of the extended primer identifies the SNP allele. (Primer sequences and reaction conditions are available upon request). Some genotyping was also done using polymerase chain reaction (PCR) endpoint analysis. All genotyping was performed blinded to case and control status.

Statistical Analysis

For each gene variant, the Haploview Program (version 4.2, http://www. broadinstitute.org/scientific-community/science/programs/ medical-and-population-genetics/haploview/haploview) [Barrett et al., 2005] was used to calculate minor allele frequency (MAF) and to evaluate deviations from Hardy–Weinberg equilibrium (HWE) among controls. These analyses were conducted for all participants together and separately for native-born Hispanic, foreign-born Hispanic, and non-Hispanic white mothers.

Of the 82 gene variants that were genotyped, five were excluded due to small sample size with both heterozygosity and homozygosity variants less than three (SCNN1A rs5742912, F2 rs1799963, F5 rs6025, TNF rs1800750, TNF rs673) among cases or controls, separately. One gene variant (ICAM5 rs892188) was excluded because it failed the HWE test (P-value <0.001, default setting in Haplovie) among all controls and among controls in each race/ethnicity group. An additional four SNPs (rs281419, rs281439, rs3093030, rs699) failed HWE among all controls, but remained in the analysis because they did fit HWE expectations when stratified by race/ethnicity. Lastly, GSTT and GSTM were combined for analysis.

Risk for gastroschisis associated with each gene variant was calculated for both the homozygotes and the heterozygotes, with the homozygous wildtypes as the referent. For all gene variants, the wild-type/reference genotype was defined as the homozygous
genotype with the most frequent allele among controls. Risks were estimated as odds ratios (ORs) with 95% confidence intervals (CIs) by logistic regression using SAS software (version 9.4, SAS Institute, Cary, NC). Regression analyses were stratified by maternal race/ethnicity, age, vitamin use, and smoking status during the peri-conceptional period (one month prior to conception through the second month of pregnancy). Wald chi-square tests were calculated for the interaction terms to determine if the subgroups were statistically different.

Haplotypes were constructed for 75 gene variants using the HaploView program (https://www.broadinstitute.org/scientific-community/science/programs/medical-and-population-genetics/haploview/haploview). The OR of each haplotype was calculated using the sum of all other haplotypes as reference.

RESULTS

The final study population included 228 individuals, 20 genes with 75 gene variants.

Demographic characteristics of cases and controls are presented in Table I. The subset of interviewed participants are in the second column. The study population was mostly Hispanic, though more cases are U.S.-born and more controls are foreign-born. Additionally, the cases are younger than controls, as expected given the increased risk for gastroschisis among young mothers.

Table II lists the position of the gene variants and summarizes the call rates and MAFs and HWE evaluation using the HaploView Program.

The results of the regression analyses in the entire population are in Supplemental Material Table I. Overall, 132 ORs were calculated. There were an additional 21 estimates that were not calculated because they did not meet our criteria which required at least three individuals in each cell. We observed 12 ORs with 95% CIs that excluded 1.0: 6 gene variants were associated with increased risk and three with decreased risk of gastroschisis for both heterozygous (ORh) and homozygous (ORv) variants. These included NOS3 (rs1036145) ORh = 0.4 (95% CI: 0.2–0.7); NOS3 (rs10277237) ORv = 2.7 (95% CI: 1.3–6.0); ADD1 (rs12503220) ORh = 2.9 (95% CI: 1.6–5.4), GNB3 (rs5443) ORh = 0.2 (95% CI: 0.1–0.5), ORv = 0.4 (95% CI: 0.2–0.9); ICAM1 (rs281428) ORh = 6.9 (95% CI: 2.1–22.9), ICAM1 (rs3093030) ORv = 2.6 (95% CI: 1.2–5.6); ICAM4 (rs281438) ORv = 4.9 (95% CI: 1.4–16.6), ICAM5

| TABLE I. Demographic Characteristics of Gastroschisis Cases and Non-Malformed Controls, California 1997–2001 |
|---------------------------------------------------------------|
| All participants (n = 228)                                    |
| Cases* (n = 79)                                              | Controls* (n = 149) |
| Maternal race/ethnicity                                      |                    |
| White                                                        | 30 (38.0)          | 52 (34.9)          |
| U.S.-born Hispanic                                           | 21 (26.6)          | 27 (18.1)          |
| Foreign-born Hispanic                                        | 19 (24.1)          | 43 (28.9)          |
| Other                                                        | 9 (11.4)           | 23 (15.4)          |
| Maternal age at delivery (years)                             |                    |
| <20                                                          | 36 (45.6)          | 22 (14.8)          |
| 20–24                                                        | 26 (32.9)          | 42 (28.2)          |
| >25                                                          | 17 (21.5)          | 81 (54.4)          |
| Maternal education (years)                                   |                    |
| <12                                                          | 38 (48.1)          | 45 (30.2)          |
| 12                                                           | 28 (35.4)          | 56 (37.6)          |
| >12                                                          | 11 (13.9)          | 42 (28.2)          |
| Parity                                                       |                    |
| 0                                                            | 53 (67.1)          | 44 (29.5)          |
| 1+                                                           | 26 (32.9)          | 101 (67.8)         |
| Plurality                                                    |                    |
| Singletons                                                   | 79 (100.0)         | 143 (96.0)         |
| Infant sex                                                   |                    |
| Male                                                         | 45 (57.0)          | 74 (49.7)          |
| Female                                                       | 34 (43.0)          | 71 (47.7)          |
| Multi-vitamin Use^b                                           |                    |
| No                                                           | N/A                | N/A                |
| Yes                                                          | N/A                | N/A                |
| Smoking^b                                                    |                    |
| None                                                         | N/A                | N/A                |
| Any                                                          | N/A                | N/A                |

N/A not applicable because interview was not conducted.
*Percentages may not equal 100 owing to rounding and missing.
^bDuring the month before or the first 2 months of pregnancy.
| Gene Symbol | dbsNP ID | Position | Reference Allele | Call rate % | MAF | HWE P * |
|-------------|----------|----------|-----------------|-------------|-----|---------|
| Homocysteine metabolism | | | | | | |
| MTHFR | rs1801133 | 11796321 | C | 97.8 | 0.35 | 0.421 |
| Blood pressure | | | | | | |
| NOS3 | rs1036145 | 150112078 | A | 96.5 | 0.29 | 0.089 |
| NOS3 | rs2373962 | 150118625 | G | 96.9 | 0.33 | 0.185 |
| NOS3 | rs6951150 | 150119562 | C | 78.9 | 0.22 | 0.031 |
| NOS3 | rs10277237 | 150120992 | G | 83.8 | 0.32 | 0.113 |
| NOS3 | rs1800783 | 150127045 | T | 100 | 0.25 | 0.528 |
| NOS3 | rs12703107 | 150683629 | G | 93.9 | 0.42 | 0.072 |
| NOS3 | rs4496877 | 150983418 | G | 99.1 | 0.24 | 1.000 |
| NOS3 | rs1800779 | 150992855 | A | 97.8 | 0.21 | 0.169 |
| NOS3 | rs3918226 | 150993088 | C | 96.1 | 0.04 | 1.000 |
| NOS3 | rs1799983 | 150999023 | G | 98.2 | 0.22 | 0.250 |
| NOS3 | rs3918227 | 151003858 | C | 94.7 | 0.05 | 0.002 |
| NOS3 | rs3918188 | 151006939 | C | 97.4 | 0.29 | 0.759 |
| NOS3 | rs743507 | 151010400 | G | 99.6 | 0.18 | 0.357 |
| AGTR1 | rs5186 | 148742201 | A | 98.2 | 0.31 | 0.271 |
| AGT | rs699 | 230710048 | T | 95.2 | 0.37 | <0.001 |
| NPPA | rs198358 | 11838342 | G | 91.7 | 0.19 | 0.001 |
| NPPA | rs198361 | 11839899 | C | 95.6 | 0.09 | 1.000 |
| NPPA | rs5067 | 11840247 | A | 100 | 0.12 | 0.643 |
| NPPA | rs198372 | 11843780 | A | 100 | 0.07 | 1.000 |
| NPPA | rs198373 | 11843801 | A | 97.8 | 0.09 | 1.000 |
| NPPA | rs632793 | 11844943 | G | 99.1 | 0.27 | 0.200 |
| NPPA | rs5065 | 11846011 | T | 98.2 | 0.13 | 1.000 |
| NPPA | rs5063 | 11847591 | G | 96.9 | 0.06 | 0.175 |
| ADD1 | rs735974 | 2809236 | C | 90.4 | 0.27 | 0.626 |
| ADD1 | rs4690002 | 2841240 | T | 100 | 0.36 | 0.117 |
| ADD1 | rs12503220 | 2850142 | G | 99.6 | 0.17 | 0.001 |
| ADD1 | rs1877723 | 2883805 | G | 91.2 | 0.22 | 0.547 |
| ADD1 | rs3775068 | 2886447 | T | 99.1 | 0.47 | 0.114 |
| ADD1 | rs10026792 | 2899196 | G | 97.4 | 0.18 | 0.162 |
| ADD1 | rs4961 | 2904980 | G | 96.9 | 0.18 | 1.000 |
| ADD1 | rs16843523 | 29155080 | C | 92.5 | 0.17 | 0.139 |
| ADD1 | rs1263359 | 2925756 | C | 97.4 | 0.13 | 0.162 |
| ADD1 | rs3775067 | 2925628 | C | 93.4 | 0.28 | 0.162 |
| ADD1 | rs7678161 | 2938608 | C | 78.9 | 0.31 | 0.004 |
| ADD1 | rs2285084 | 2943293 | C | 100 | 0.21 | 0.059 |
| ADD1 | rs762847 | 2949071 | C | 95.2 | 0.44 | 0.003 |
| SCNN1A | rs2228576 | 6327323 | G | 95.6 | 0.29 | 0.905 |
| GNB3 | rs5443 | 6845711 | C | 96.1 | 0.38 | 0.337 |
| ADRB2 | rs1042713 | 14882687 | A | 96.1 | 0.48 | 0.233 |
| ADRB2 | rs1042714 | 148826910 | C | 95.6 | 0.18 | 0.034 |
| Coagulation | | | | | | |
| F7 | rs5742910 | 113105517 | Deletion | 98.2 | 0.14 | 1.000 |
| F7 | rs6064 | 113118845 | G | 94.3 | 0.11 | 1.000 |
| SERPINE1 | rs2227684 | 100776391 | G | 97.8 | 0.36 | 0.302 |
| FGB | rs1799768 | 100785547 | G | 97.8 | 0.17 | 0.323 |
| SERPINE1 | rs1799889 | 101124630 | G | 97.8 | 0.41 | 0.636 |
| Cell–cell interaction | | | | | | |
| ITGA2 | rs1062535 | 52351413 | G | 98.2 | 0.37 | 0.180 |
| ITGB3 | rs5918 | 45360730 | T | 98.2 | 0.10 | 0.756 |
| SELE | rs5355 | 16927629 | C | 98.2 | 0.04 | 1.000 |
The only significant results stratified by smoking were among non-smokers. Owing to the low proportion of smokers, there was insufficient statistical power to reasonably estimate several ORs among smokers. A decreased risk of gastroschisis was observed among non-smoking mothers whose infants were heterozygous for ADD1 (rs7678161) and NPPA (rs5065).

Haplotype blocks were constructed using the HaploView program. In general, reconstruction of the SNPs did not show evidence of nonrandom association with gastroschisis (Table IV), which may have been a function of small sample size.

**DISCUSSION**

This California population-based study observed increased risks of gastroschisis for infants who had variants in genes related to blood pressure and cell–cell interaction. Homozygous and heterozygous variants of two genes related to blood pressure (NOS3 and ADD1), were associated with increased risks of gastroschisis. Several homozygous and heterozygous variants in the cell–cell interaction pathogenetic grouping were associated with increased risks of gastroschisis. ICAM1, ICAM4, and several ICAM5 variants significant associations with gastroschisis, including one ICAM5 variant with a strong, but statistically limited association. Additionally, variants of GNB3 and NAT1 showed decreased risk for gastroschisis.
### TABLE III. Associations Between Gene Variants and Risk of Gastroschisis Stratified by Selected Maternal Demographics and Exposures, California 1997–2001

| Gene Symbol | dbSNP ID   | Subgroup       | Genotype | Case N | Control N | OR (95% CI)   |
|-------------|------------|----------------|----------|--------|-----------|---------------|
| MTHFR       | rs1801133  | White NH       | Wildtype | 10     | 20        | Reference     |
| MTHFR       | rs1801133  | White NH       | Hetero   | 16     | 22        | 1.2 (0.4–3.2) |
| MTHFR       | rs1801133  | White NH       | Variant  | 3      | 5         | 1.2 (0.2–6.1) |
| MTHFR       | rs1801133  | NB Hispanic    | Wildtype | 3      | 15        | Reference     |
| MTHFR       | rs1801133  | NB Hispanic    | Hetero   | 13     | 8         | 8.1 (1.8–37.2) |
| MTHFR       | rs1801133  | NB Hispanic    | Variant  | 3      | 3         | 5.0 (0.7–37.8) |
| MTHFR       | rs1801133  | FB Hispanic    | Wildtype | 3      | 13        | Reference     |
| MTHFR       | rs1801133  | FB Hispanic    | Hetero   | 10     | 20        | 2.2 (0.5–9.4)  |
| MTHFR       | rs1801133  | FB Hispanic    | Variant  | 6      | 10        | 2.6 (0.5–13.0) |
| NOS3        | rs1036145  | White NH       | Wildtype | 15     | 19        | Reference     |
| NOS3        | rs1036145  | White NH       | Hetero   | 8      | 28        | 0.4 (0.1–1.0) |
| NOS3        | rs1036145  | White NH       | Variant  | 5      | 4         | 1.6 (0.4–6.9) |
| NOS3        | rs1036145  | NB Hispanic    | Wildtype | 14     | 17        | Reference     |
| NOS3        | rs1036145  | NB Hispanic    | Hetero   | 5      | 6         | 1.0 (0.3–4.0) |
| NOS3        | rs1036145  | NB Hispanic    | Variant  | 1      | 1         | Reference     |
| NOS3        | rs1036145  | FB Hispanic    | Wildtype | 11     | 19        | Reference     |
| NOS3        | rs1036145  | FB Hispanic    | Hetero   | 4      | 23        | 0.3 (0.1–1.1) |
| NOS3        | rs1036145  | FB Hispanic    | Variant  | 4      | 1         | Reference     |
| NOS3        | rs3918188  | White NH       | Wildtype | 13     | 25        | Reference     |
| NOS3        | rs3918188  | White NH       | Hetero   | 11     | 19        | 1.1 (0.4–3.0) |
| NOS3        | rs3918188  | White NH       | Variant  | 5      | 7         | 1.4 (0.4–5.2) |
| NOS3        | rs3918188  | NB Hispanic    | Wildtype | 14     | 17        | Reference     |
| NOS3        | rs3918188  | NB Hispanic    | Hetero   | 5      | 8         | 0.8 (0.2–2.8) |
| NOS3        | rs3918188  | NB Hispanic    | Variant  | 1      | 0         | Reference     |
| NOS3        | rs3918188  | FB Hispanic    | Wildtype | 5      | 25        | 3.2 (1.0–11.0) |
| NOS3        | rs3918188  | FB Hispanic    | Hetero   | 11     | 17        | Reference     |
| NOS3        | rs3918188  | FB Hispanic    | Variant  | 3      | 1         | Reference     |
| AGT         | rs699      | White NH       | Wildtype | 6      | 12        | Reference     |
| AGT         | rs699      | White NH       | Hetero   | 17     | 25        | 1.4 (0.4–4.3) |
| AGT         | rs699      | White NH       | Variant  | 4      | 14        | 0.6 (0.1–2.5) |
| AGT         | rs699      | NB Hispanic    | Wildtype | 8      | 11        | Reference     |
| AGT         | rs699      | NB Hispanic    | Hetero   | 8      | 11        | 1.0 (0.3–3.6) |
| AGT         | rs699      | NB Hispanic    | Variant  | 4      | 3         | 1.8 (0.3–10.6) |
| AGT         | rs699      | FB Hispanic    | Wildtype | 7      | 24        | Reference     |
| AGT         | rs699      | FB Hispanic    | Hetero   | 8      | 6         | 4.6 (1.2–17.7) |
| AGT         | rs699      | FB Hispanic    | Variant  | 4      | 11        | 1.2 (0.3–5.2) |
| ADD1        | rs12503220 | White NH       | Wildtype | 19     | 41        | Reference     |
| ADD1        | rs12503220 | White NH       | Hetero   | 10     | 8         | 2.7 (0.9–7.9) |
| ADD1        | rs12503220 | White NH       | Variant  | 1      | 3         | Reference     |
| ADD1        | rs12503220 | NB Hispanic    | Wildtype | 7      | 17        | Reference     |
| ADD1        | rs12503220 | NB Hispanic    | Hetero   | 12     | 7         | Reference     |
| ADD1        | rs12503220 | NB Hispanic    | Variant  | 2      | 2         | Reference     |
| ADD1        | rs12503220 | FB Hispanic    | Wildtype | 10     | 32        | Reference     |
| ADD1        | rs12503220 | FB Hispanic    | Hetero   | 6      | 7         | 2.7 (0.7–10.1) |
| ADD1        | rs12503220 | FB Hispanic    | Variant  | 3      | 4         | 2.4 (0.5–12.6) |
| GNB3        | Rs5443     | White NH       | Wildtype | 22     | 28        | Reference     |
| GNB3        | Rs5443     | White NH       | Hetero   | 5      | 18        | 0.4 (0.1–1.1) |
| GNB3        | Rs5443     | White NH       | Variant  | 2      | 5         | Reference     |
| GNB3        | Rs5443     | NB Hispanic    | Wildtype | 14     | 9         | Reference     |
| GNB3        | Rs5443     | NB Hispanic    | Hetero   | 4      | 13        | Reference     |
| GNB3        | Rs5443     | NB Hispanic    | Variant  | 2      | 3         | Reference     |
| GNB3        | Rs5443     | FB Hispanic    | Wildtype | 13     | 17        | Reference     |
| GNB3        | Rs5443     | FB Hispanic    | Hetero   | 4      | 15        | 0.2 (0.0–0.8) |
| GNB3        | Rs5443     | FB Hispanic    | Variant  | 2      | 10        | Reference     |
| Gene Symbol | dbSNP ID | Subgroup   | Genotype | Case N | Control N | OR (95% CI) |
|-------------|---------|------------|----------|--------|-----------|-------------|
| SERPINE1    | rs1799889 | White NH | Wildtype | 10     | 8         | Reference   |
| SERPINE1    | rs1799889 | White NH | Hetero   | 15     | 27        | 0.4 [0.1–1.4] |
| SERPINE1    | rs1799889 | White NH | Variant  | 4      | 16        | 0.2 [0.0–0.8] |
| SERPINE1    | rs1799889 | NB Hispanic | Wildtype | 10     | 12        | 1.1 [0.3–3.7] |
| SERPINE1    | rs1799889 | NB Hispanic | Hetero | 9      | 10        | Reference   |
| SERPINE1    | rs1799889 | NB Hispanic | Variant | 1      | 4         | NC          |
| SERPINE1    | rs1799889 | FB Hispanic | Wildtype | 9      | 23        | Reference   |
| SERPINE1    | rs1799889 | FB Hispanic | Hetero | 7      | 17        | 1.1 [0.3–3.4] |
| SERPINE1    | rs1799889 | FB Hispanic | Variant | 3      | 3         | 2.6 [0.4–15.1] |
| SELE        | rs5361   | White NH | Wildtype | 21     | 46        | Reference   |
| SELE        | rs5361   | White NH | Hetero   | 8      | 4         | Reference   |
| SELE        | rs5361   | White NH | Variant  | 0      | 2         | NC          |
| SELE        | rs5361   | NB Hispanic | Wildtype | 19     | 26        | Reference   |
| SELE        | rs5361   | NB Hispanic | Hetero | 1      | 0         | NC          |
| SELE        | rs5361   | NB Hispanic | Variant | 0      | 0         | NC          |
| SELE        | rs5361   | FB Hispanic | Wildtype | 19     | 38        | Reference   |
| SELE        | rs5361   | FB Hispanic | Hetero | 0      | 5         | NC          |
| ICAM1       | rs11115  | White NH | Wildtype | 12     | 24        | Reference   |
| ICAM1       | rs11115  | White NH | Hetero   | 12     | 18        | 1.3 [0.5–3.6] |
| ICAM1       | rs11115  | NB Hispanic | Wildtype | 6      | ?         | Reference   |
| ICAM1       | rs11115  | NB Hispanic | Hetero | 10     | 13        | 1.0 [0.3–3.6] |
| ICAM1       | rs11115  | NB Hispanic | Variant | 3      | 5         | Reference   |
| ICAM1       | rs11115  | FB Hispanic | Wildtype | 1      | 14        | Reference   |
| ICAM1       | rs11115  | FB Hispanic | Hetero | 13     | 17        | Reference   |
| ICAM1       | rs3093030 | White NH | Wildtype | 9      | 24        | Reference   |
| ICAM1       | rs3093030 | White NH | Hetero   | 8      | 10        | 2.1 [0.6–7.1] |
| ICAM1       | rs3093030 | White NH | Variant  | 11     | 9         | 3.3 [1.0–10.5] |
| ICAM1       | rs3093030 | NB Hispanic | Wildtype | 13     | 12        | Reference   |
| ICAM1       | rs3093030 | NB Hispanic | Hetero | 3      | 5         | 0.6 [0.1–2.8] |
| ICAM1       | rs3093030 | NB Hispanic | Variant | 3      | 2         | NC          |
| ICAM1       | rs3093030 | FB Hispanic | Wildtype | 7      | 24        | Reference   |
| ICAM1       | rs3093030 | FB Hispanic | Hetero | 2      | ?         | NC          |
| ICAM1       | rs3093030 | FB Hispanic | Variant | 3      | 2         | NC          |
| ICAM1       | rs281440  | White NH | Wildtype | 2      | 22        | Reference   |
| ICAM1       | rs281440  | White NH | Hetero   | 14     | 19        | 8.1 [1.6–40.3] |
| ICAM1       | rs281440  | White NH | Variant  | 3      | 4         | 8.2 [1.0–66.2] |
| ICAM1       | rs281440  | NB Hispanic | Wildtype | 0      | 11        | Reference   |
| ICAM1       | rs281440  | NB Hispanic | Hetero | 13     | 9         | NC          |
| ICAM1       | rs281440  | NB Hispanic | Variant | 0      | 0         | NC          |
| ICAM1       | rs281440  | FB Hispanic | Wildtype | 0      | 18        | Reference   |
| ICAM1       | rs281440  | FB Hispanic | Hetero | 11     | 22        | NC          |
| ICAM1       | rs281440  | FB Hispanic | Variant | 1      | 1         | NC          |
| ICAM1       | rs2075741 | White NH | Wildtype | 6      | 13        | Reference   |
| ICAM1       | rs2075741 | White NH | Hetero   | 8      | 23        | 0.8 [0.2–2.7] |
| ICAM1       | rs2075741 | White NH | Variant  | 15     | 16        | 2.0 [0.6–6.7] |
| ICAM1       | rs2075741 | NB Hispanic | Wildtype | 7      | 13        | Reference   |
| ICAM1       | rs2075741 | NB Hispanic | Hetero | 9      | 6         | 2.8 [0.7–11.1] |
| ICAM1       | rs2075741 | NB Hispanic | Variant | 4      | 6         | 1.2 [0.3–5.9] |
| ICAM1       | rs2075741 | FB Hispanic | Wildtype | 6      | 23        | Reference   |
| ICAM1       | rs2075741 | FB Hispanic | Hetero | 6      | 14        | 1.6 [0.4–6.1] |
| ICAM1       | rs2075741 | FB Hispanic | Variant | 5      | 4         | 4.8 [1.0–23.6] |
| ICAM1       | rs2569702 | White NH | Wildtype | 16     | 16        | Reference   |
| ICAM1       | rs2569702 | White NH | Hetero   | 10     | 28        | 0.4 [0.1–1.0] |
| ICAM1       | rs2569702 | White NH | Variant  | 4      | 8         | 0.5 [0.1–2.0] |
| ICAM1       | rs2569702 | NB Hispanic | Wildtype | 5      | 8         | Reference   |
| ICAM1       | rs2569702 | NB Hispanic | Hetero | 11     | 10        | 1.8 [0.4–7.2] |
| Gene Symbol | dbSNP ID | Subgroup | Genotype | Case N | Control N | OR (95% CI) |
|-------------|----------|----------|----------|--------|-----------|-------------|
| ICAM5       | rs2569702 | NB Hispanic | Variant | 5      | 9         | 0.9 (0.2–4.2) |
| ICAM5       | rs2569702 | FB Hispanic | Wildtype | 5      | 9         | Reference   |
| ICAM5       | rs2569702 | FB Hispanic | Hetero   | 8      | 16        | 0.9 (0.2–3.6) |
| ICAM5       | rs2569702 | FB Hispanic | Variant  | 6      | 18        | 0.6 (0.1–2.5) |
| MTHFR       | rs1801133 | Age <20 Wildtype | 12 | 9 | Reference |
| MTHFR       | rs1801133 | Age <20 Hetero | 16 | 10 | 1.2 (0.4–3.9) |
| MTHFR       | rs1801133 | Age <20 Variant | 7 | 2 | NC |
| MTHFR       | rs1801133 | Age 20–24 Wildtype | 7 | 18 | Reference |
| MTHFR       | rs1801133 | Age 20–24 Hetero | 12 | 15 | 2.1 (0.6–6.5) |
| MTHFR       | rs1801133 | Age 20–24 Variant | 5 | 9 | 1.4 (0.4–5.8) |
| MTHFR       | rs1801133 | Age 25+ Wildtype | 4 | 36 | Reference |
| MTHFR       | rs1801133 | Age 25+ Hetero | 13 | 35 | 3.3 (1.0–11.2) |
| MTHFR       | rs1801133 | Age 25+ Variant | 0 | 9 | NC |
| NOS3        | rs1800779 | Age <20 Wildtype | 24 | 15 | Reference |
| NOS3        | rs1800779 | Age <20 Hetero | 10 | 3 | 2.1 (0.5–8.8) |
| NOS3        | rs1800779 | Age <20 Variant | 1 | 3 | NC |
| NOS3        | rs1800779 | Age 20–24 Wildtype | 10 | 32 | Reference |
| NOS3        | rs1800779 | Age 20–24 Hetero | 10 | 9 | 3.6 (1.1–11.2) ** |
| NOS3        | rs1800779 | Age 20–24 Variant | 4 | 1 | NC |
| NOS3        | rs2137962 | Age <20 Wildtype | 10 | 32 | Reference |
| NOS3        | rs2137962 | Age <20 Hetero | 10 | 7 | 4.6 (1.4–15.2) ** |
| NOS3        | rs2137962 | Age <20 Variant | 4 | 2 | NC |
| NOS3        | rs237962  | Age 20–24 Wildtype | 12 | 42 | Reference |
| NOS3        | rs237962  | Age 20–24 Hetero | 3 | 29 | 0.4 (0.1–1.4) |
| NOS3        | rs237962  | Age 20–24 Variant | 1 | 7 | NC |
| NOS3        | rs3918188 | Age <20 Wildtype | 20 | 11 | Reference |
| NOS3        | rs3918188 | Age <20 Hetero | 14 | 8 | 1.0 (0.3–3.0) |
| NOS3        | rs3918188 | Age <20 Variant | 0 | 3 | NC |
| NOS3        | rs3918188 | Age 20–24 Wildtype | 13 | 19 | Reference |
| NOS3        | rs3918188 | Age 20–24 Hetero | 9 | 15 | 0.9 (0.3–2.6) |
| NOS3        | rs3918188 | Age 20–4 Variant | 4 | 4 | 1.5 (0.3–6.9) |
| NOS3        | rs3918188 | Age 20–24 Wildtype | 5 | 43 | Reference |
| NOS3        | rs3918188 | Age 20–24 Hetero | 7 | 32 | 1.9 (0.5–6.5) |
| NOS3        | rs3918188 | Age 20–24 Variant | 5 | 6 | 7.2 (1.6–32.3) |
| NOS3        | rs4496877 | Age <20 Wildtype | 24 | 13 | Reference |
| NOS3        | rs4496877 | Age <20 Hetero | 12 | 8 | 0.8 (0.3–2.5) |
| NOS3        | rs4496877 | Age <20 Variant | 0 | 1 | NC |
| NOS3        | rs4496877 | Age 20–24 Wildtype | 11 | 31 | Reference |
| NOS3        | rs4496877 | Age 20–24 Hetero | 11 | 9 | 3.4 (1.1–10.5) ** |
| NOS3        | rs4496877 | Age 20–4 Variant | 3 | 1 | NC |
| NOS3        | rs4496877 | Age 20–24 Wildtype | 12 | 40 | Reference |
| NOS3        | rs4496877 | Age 20–4 Hetero | 4 | 35 | 0.4 (0.1–1.3) |
| NOS3        | rs4496877 | Age 20–4 Variant | 1 | 6 | NC |
| NOS3        | rs6951150 | Age <20 Wildtype | 21 | 11 | Reference |
| NOS3        | rs6951150 | Age <20 Hetero | 9 | 6 | 0.8 (0.2–2.8) |
| NOS3        | rs6951150 | Age <20 Variant | 0 | 2 | NC |
| NOS3        | rs6951150 | Age 20–24 Wildtype | 10 | 26 | Reference |
| NOS3        | rs6951150 | Age 20–24 Hetero | 10 | 6 | 4.3 (1.2–15.1) |
| NOS3        | rs6951150 | Age 20–24 Variant | 3 | 2 | NC |
| NOS3        | rs6951150 | Age 25+ Wildtype | 10 | 35 | Reference |
| NOS3        | rs6951150 | Age 25+ Hetero | 3 | 17 | 0.6 (0.2–2.5) |

(Continued)
| Gene Symbol | dbSNP ID   | Subgroup | Genotype | Case N | Control N | OR (95% CI) |
|-------------|------------|----------|----------|--------|-----------|-------------|
| NOS3        | rs6951150  | Age 25+  | Variant  | 1      | 6         | Reference   |
| ADD1        | rs2285084  | Age <20  | Wildtype | 26     | 13        | 0.6 [0.2–1.9] |
| ADD1        | rs2285084  | Age <20  | Hetero   | 8      | ?         | Reference   |
| ADD1        | rs2285084  | Age <20  | Variant  | 2      | 2         | Reference   |
| ADD1        | rs2285084  | Age 20–24| Wildtype | 17     | 29        | 1.7 [0.5–5.4] |
| ADD1        | rs2285084  | Age 20–24| Hetero   | 8      | 8         | Reference   |
| ADD1        | rs2285084  | Age 20–24| Variant  | 1      | 5         | Reference   |
| ADD1        | rs2285084  | Age 25+  | Wildtype | 6      | 51        | 2.6 [0.8–8.3] |
| ADD1        | rs2285084  | Age 25+  | Hetero   | 8      | 26        | 6.4 [1.1–35.6] |
| ADD1        | rs2285084  | Age 25+  | Variant  | 3      | 4         | Reference   |
| ADD1        | rs2285084  | Age 25+  | Wildtype | 10     | 23        | Reference   |
| ADD1        | rs2285084  | Age 25+  | Hetero   | 11     | 8         | Reference   |
| ADD1        | rs2285084  | Age 25+  | Variant  | 1      | 2         | Reference   |
| ADD1        | rs7678161  | Age <20  | Wildtype | 6      | 16        | 1.2 [0.3–3.9] |
| ADD1        | rs7678161  | Age <20  | Hetero   | 11     | 8         | Reference   |
| ADD1        | rs7678161  | Age <20  | Variant  | 2      | NC        | Reference   |
| ADD1        | rs7678161  | Age 20–24| Wildtype | 8      | 17        | 1.3 [0.4–4.4] |
| ADD1        | rs7678161  | Age 20–24| Hetero   | 1      | 1         | Reference   |
| ADD1        | rs7678161  | Age 20–24| Variant  | 2      | NC        | Reference   |
| ADD1        | rs7678161  | Age 20–24| Wildtype | 10     | 23        | Reference   |
| ADD1        | rs7678161  | Age 20–24| Hetero   | 5      | 42        | Reference   |
| ADD1        | rs7678161  | Age 20–24| Variant  | 0      | 2         | Reference   |
| ADD1        | rs12503220 | Age <20  | Wildtype | 20     | 14        | 2.8 [0.9–9.1] |
| ADD1        | rs12503220 | Age <20  | Hetero   | 12     | 5         | Reference   |
| ADD1        | rs12503220 | Age <20  | Variant  | 4      | 3         | Reference   |
| ADD1        | rs12503220 | Age 20–24| Wildtype | 12     | 29        | Reference   |
| ADD1        | rs12503220 | Age 20–24| Hetero   | 14     | ?         | Reference   |
| ADD1        | rs12503220 | Age 20–24| Variant  | 0      | 5         | Reference   |
| ADD1        | rs12503220 | Age 25+  | Wildtype | 9      | 63        | Reference   |
| ADD1        | rs12503220 | Age 25+  | Hetero   | 6      | 15        | Reference   |
| ADD1        | rs12503220 | Age 25+  | Variant  | 2      | 3         | Reference   |
| ADD1        | rs16843523 | Age <20  | Wildtype | 25     | 13        | Reference   |
| ADD1        | rs16843523 | Age <20  | Hetero   | 7      | 6         | Reference   |
| ADD1        | rs16843523 | Age <20  | Variant  | 3      | 2         | Reference   |
| ADD1        | rs16843523 | Age 20–24| Wildtype | 17     | 29        | Reference   |
| ADD1        | rs16843523 | Age 20–24| Hetero   | 6      | 8         | Reference   |
| ADD1        | rs16843523 | Age 20–24| Variant  | 3      | 2         | Reference   |
| ADD1        | rs16843523 | Age 25+  | Wildtype | 8      | 50        | Reference   |
| ADD1        | rs16843523 | Age 25+  | Hetero   | 3      | 19        | Reference   |
| ADD1        | rs16843523 | Age 25+  | Variant  | 3      | 3         | Reference   |
| GNB3        | rs5443     | Age <20  | Wildtype | 25     | 6         | Reference   |
| GNB3        | rs5443     | Age <20  | Hetero   | 7      | 8         | 0.2 [0.1–0.8] |
| GNB3        | rs5443     | Age <20  | Variant  | 3      | 6         | 0.1 [0.0–0.6] |
| GNB3        | rs5443     | Age 20–24| Wildtype | 18     | 17        | 0.2 [0.0–0.7] |
| GNB3        | rs5443     | Age 20–24| Hetero   | 3      | 17        | 0.5 [0.1–2.2] |
| GNB3        | rs5443     | Age 20–24| Variant  | 4      | ?         | Reference   |
| GNB3        | rs5443     | Age 25+  | Wildtype | 11     | 32        | 0.3 [0.1–1.2] |
| GNB3        | rs5443     | Age 25+  | Hetero   | 4      | 34        | Reference   |
| GNB3        | rs5443     | Age 25+  | Variant  | 2      | 11        | Reference   |
| ADRB2       | rs1042714  | Age <20  | Wildtype | 26     | 17        | Reference   |
| ADRB2       | rs1042714  | Age <20  | Hetero   | 6      | 4         | 1.0 [0.2–4.0] |
| ADRB2       | rs1042714  | Age <20  | Variant  | 1      | 0         | Reference   |
| ADRB2       | rs1042714  | Age 20–24| Wildtype | 20     | 23        | Reference   |
| ADRB2       | rs1042714  | Age 20–24| Hetero   | 3      | 14        | 0.2 [0.1–1.0] |
| ADRB2       | rs1042714  | Age 20–24| Variant  | 1      | 4         | Reference   |
| ADRB2       | rs1042714  | Age 25+  | Wildtype | 14     | 58        | Reference   |
| ADRB2       | rs1042714  | Age 25+  | Hetero   | 2      | 16        | Reference   |
| ADRB2       | rs1042714  | Age 25+  | Variant  | 0      | 5         | Reference   |
| ICAM1       | rs281432   | Age <20  | Wildtype | 13     | ?         | Reference   |
| ICAM1       | rs281432   | Age <20  | Hetero   | 12     | 8         | 0.8 [0.2–2.9] |
| ICAM1       | rs281432   | Age <20  | Variant  | 10     | 4         | 1.3 [0.3–5.9] |
| ICAM1       | rs281432   | Age 20–24| Wildtype | 9      | 18        | Reference   |

(Continued)
| Gene Symbol | dbSNP ID | Subgroup | Genotype | Case N | Control N | OR (95% CI) |
|-------------|----------|----------|----------|--------|-----------|-------------|
| ICAM1       | rs281432 | Age 20–24| Hetero   | 6      | 15        | 0.8 [0.2–2.8] |
| ICAM1       | rs281432 | Age 20–24| Variant  | 9      | 7         | 2.6 [0.7–9.2] |
| ICAM1       | rs281432 | Age 25+  | Wildtype | 9      | 22        | Reference    |
| ICAM1       | rs1059849| Age <20  | Hetero   | 4      | 41        | 0.2 [0.1–0.9] |
| ICAM1       | rs1059849| Age <20  | Variant  | 3      | 14        | 0.5 [0.1–2.3] |
| ICAM1       | rs1059849| Age 20–24| Wildtype | 9      | 14        | Reference    |
| ICAM1       | rs1059849| Age 20–24| Variant  | 3      | 13        | 0.5 [0.1–2.3] |
| ICAM1       | rs1059849| Age 25+  | Wildtype | 3      | 14        | Reference    |
| ICAM1       | rs1059849| Age 25+  | Hetero   | 8      | 37        | 2.2 [0.5–9.2] |
| ICAM1       | rs1059849| Age 25+  | Variant  | 5      | 11        | Reference    |
| ICAM5       | rs281440 | Age <20  | Wildtype | 1      | 13        | Reference    |
| ICAM5       | rs281440 | Age <20  | Hetero   | 15     | 6         | Reference    |
| ICAM5       | rs281440 | Age <20  | Variant  | 3      | 1         | Reference    |
| ICAM5       | rs281440 | Age 20–24| Wildtype | 1      | 11        | Reference    |
| ICAM5       | rs281440 | Age 20–24| Hetero   | 15     | 20        | Reference    |
| ICAM5       | rs281440 | Age 20–24| Variant  | 0      | 3         | Reference    |
| ICAM5       | rs281440 | Age 25+  | Wildtype | 0      | 39        | Reference    |
| ICAM5       | rs281440 | Age 25+  | Hetero   | 8      | 31        | Reference    |
| ICAM5       | rs281440 | Age 25+  | Variant  | 2      | 3         | Reference    |
| GSTT1 & GSTM1 | rs281440 | Age <20  | No Null  | 17     | 8         | Reference    |
| GSTT1 & GSTM1 | rs281440 | Age <20  | Null in M| 11     | 10        | 0.5 [0.2–1.7] |
| GSTT1 & GSTM1 | rs281440 | Age <20  | Null in T| 3      | 1         | Reference    |
| GSTT1 & GSTM1 | rs281440 | Age 20–24| No Null  | 10     | 21        | 0.8 [0.1–4.1] |
| GSTT1 & GSTM1 | rs281440 | Age 20–24| Null in M| 13     | 9         | Reference    |
| GSTT1 & GSTM1 | rs281440 | Age 20–24| Null in T| 2      | 8         | Reference    |
| GSTT1 & GSTM1 | rs281440 | Age 20–24| Both Null| 1      | 4         | Reference    |
| GSTT1 & GSTM1 | rs281440 | Age 25+  | No Null  | 8      | 45        | Reference    |
| GSTT1 & GSTM1 | rs281440 | Age 25+  | Null in M| 7      | 27        | 1.5 [0.5–4.5] |
| GSTT1 & GSTM1 | rs281440 | Age 25+  | Null in T| 1      | 7         | Reference    |
| GSTT1 & GSTM1 | rs281440 | Age 25+  | Both Null| 0      | 2         | Reference    |
| MTHFR       | rs1801133| Vitamin use| Wildtype | 7      | 29        | Reference    |
| MTHFR       | rs1801133| Vitamin use| Hetero   | 22     | 28        | 3.3 [1.2–8.8] |
| MTHFR       | rs1801133| Vitamin use| Variant  | 4      | 11        | 1.5 [0.4–6.2] |
| MTHFR       | rs1801133| No vitamin use| Wildtype | 9      | 12        | Reference    |
| MTHFR       | rs1801133| No vitamin use| Hetero   | 13     | 20        | 0.9 [0.3–2.6] |
| NOS3        | rs1036145| Vitamin use| Wildtype | 22     | 28        | Reference    |
| NOS3        | rs1036145| Vitamin use| Hetero   | 7      | 36        | 0.2 [0.1–0.7] |
| NOS3        | rs1036145| Vitamin use| Variant  | 4      | 3         | 1.7 [0.3–8.4] |
| NOS3        | rs1036145| No vitamin use| Wildtype | 16     | 19        | Reference    |
| NOS3        | rs1036145| No vitamin use| Hetero   | 7      | 14        | 0.6 [0.2–1.8] |
| NOS3        | rs1036145| No vitamin use| Variant  | 4      | 3         | 1.6 [0.3–8.1] |
| NOS3        | rs10277237| Vitamin use| Wildtype | 8      | 26        | Reference    |
| NOS3        | rs10277237| Vitamin use| Hetero   | 10     | 25        | 1.3 [0.4–3.8] |
| NOS3        | rs10277237| Vitamin use| Variant  | 11     | 7         | Reference    |
| NOS3        | rs10277237| No vitamin use| Wildtype | 7      | 12        | 1.0 [0.3–3.6] |
| NOS3        | rs10277237| No vitamin use| Hetero   | 9      | 15        | 2.4 [0.5–10.5] |
| AGT         | rs699     | Vitamin use| Hetero   | 17     | 20        | 2.6 [1.0–6.9] |
| AGT         | rs699     | Vitamin use| Variant  | 5      | 16        | 1.0 [0.3–3.3] |
| AGT         | rs699     | No vitamin use| Wildtype | 13     | 14        | Reference    |

[Continued]
| Gene Symbol | dbsNP ID | Subgroup | Genotype | Case N | Control N | OR (95% CI) |
|-------------|---------|----------|----------|--------|-----------|-------------|
| AGT         | rs699   | No vitamin use | Hetero   | 11     | 16        | 0.7 (0.3–2.2) |
| AGT         | rs699   | No vitamin use | Variant  | 3      | 6         | 0.5 (0.1–2.6) |
| ADD1        | rs7678161 | Vitamin use | Wildtype | 17     | 24        | Reference    |
| ADD1        | rs7678161 | Vitamin use | Hetero   | 5      | 32        | 0.2 (0.1–0.7)** |
| ADD1        | rs7678161 | Vitamin use | Variant  | 1      | 1         | Reference    |
| ADD1        | rs7678161 | No vitamin use | Wildtype | 7      | 13        | Reference    |
| ADD1        | rs7678161 | No vitamin use | Hetero   | 14     | 17        | 1.5 (0.5–4.9) |
| ADD1        | rs7678161 | No vitamin use | Variant  | 1      | 1         | Reference    |
| ADD1        | rs10026792 | Vitamin use | Wildtype | 26     | 48        | Reference    |
| ADD1        | rs10026792 | Vitamin use | Hetero   | 6      | 18        | 0.6 (0.2–1.7) |
| ADD1        | rs10026792 | Vitamin use | Variant  | 2      | 2         | Reference    |
| ADD1        | rs10026792 | No vitamin use | Wildtype | 12     | 25        | Reference    |
| ADD1        | rs10026792 | No vitamin use | Hetero   | 13     | 8         | 3.4 (1.1–10.4)** |
| ADD1        | rs12503220 | Vitamin use | Wildtype | 18     | 53        | Reference    |
| ADD1        | rs12503220 | Vitamin use | Hetero   | 14     | 12        | 3.4 (1.3–8.8) |
| ADD1        | rs12503220 | Vitamin use | Variant  | 3      | 4         | Reference    |
| ADD1        | rs12503220 | No vitamin use | Wildtype | 13     | 25        | Reference    |
| ADD1        | rs12503220 | No vitamin use | Hetero   | 13     | 10        | 2.5 (0.9–7.2) |
| SCNN1A      | rs2228576 | Vitamin use | Wildtype | 13     | 37        | Reference    |
| SCNN1A      | rs2228576 | Vitamin use | Hetero   | 15     | 23        | 1.9 (0.7–4.6) |
| SCNN1A      | rs2228576 | Vitamin use | Variant  | 5      | 5         | 2.8 (0.7–11.4) |
| SCNN1A      | rs2228576 | No vitamin use | Wildtype | 18     | 13        | Reference    |
| SCNN1A      | rs2228576 | No vitamin use | Hetero   | 7      | 20        | 0.3 (0.1–0.8)** |
| SCNN1A      | rs2228576 | No vitamin use | Variant  | 2      | 4         | Reference    |
| GNB3        | Rs5443   | Vitamin use | Wildtype | 24     | 26        | Reference    |
| GNB3        | Rs5443   | Vitamin use | Hetero   | 5      | 31        | 0.2 (0.1–0.5) |
| GNB3        | Rs5443   | Vitamin use | Variant  | 4      | 9         | 0.5 (0.1–1.8) |
| GNB3        | Rs5443   | No vitamin use | Wildtype | 19     | 17        | Reference    |
| GNB3        | Rs5443   | No vitamin use | Hetero   | 5      | 13        | 0.3 (0.1–1.2) |
| GNB3        | Rs5443   | No vitamin use | Variant  | 3      | 6         | 0.4 (0.1–2.1) |
| ICAM1       | rs281432  | Vitamin use | Wildtype | 13     | 18        | Reference    |
| ICAM1       | rs281432  | Vitamin use | Hetero   | 8      | 33        | Reference    |
| ICAM1       | rs281432  | Vitamin use | Variant  | 11     | 14        | 0.3 (0.1–1.0)* |
| ICAM1       | rs281432  | No vitamin use | Wildtype | 10     | 18        | Reference    |
| ICAM1       | rs281432  | No vitamin use | Hetero   | 11     | 9         | 1.1 (0.4–3.2) |
| ICAM1       | rs281432  | No vitamin use | Variant  | 6      | 5         | 2.2 (0.7–7.1) |
| ICAM1       | rs3093030 | Vitamin use | Wildtype | 16     | 30        | 2.2 (0.5–8.9) |
| ICAM1       | rs3093030 | Vitamin use | Hetero   | 6      | 13        | Reference    |
| ICAM1       | rs3093030 | Vitamin use | Variant  | 8      | 9         | 0.9 (0.3–2.7) |
| ICAM1       | rs3093030 | No vitamin use | Wildtype | 10     | 23        | 1.7 (0.5–5.2) |
| ICAM1       | rs3093030 | No vitamin use | Hetero   | 4      | 5         | Reference    |
| ICAM1       | rs3093030 | No vitamin use | Variant  | 10     | 3         | 1.8 (0.4–8.3) |
| ICAM1       | rs3093030 | No vitamin use | Variant  | 10     | 3         | 7.7 (1.7–34.0) |
| ICAM4       | rs281438  | Vitamin use | Wildtype | 22     | 45        | Reference    |
| ICAM4       | rs281438  | Vitamin use | Hetero   | 6      | 19        | 0.6 (0.2–1.8) |
| ICAM4       | rs281438  | Vitamin use | Variant  | 5      | 2         | Reference    |
| ICAM4       | rs281438  | No vitamin use | Wildtype | 14     | 31        | Reference    |
| ICAM4       | rs281438  | No vitamin use | Hetero   | 11     | 5         | 4.9 (1.4–16.7)** |
| ICAM4       | rs281438  | No vitamin use | Variant  | 2      | 1         | Reference    |
| ICAM5       | rs281438  | Vitamin use | Wildtype | 9      | 22        | Reference    |
| ICAM5       | rs281438  | Vitamin use | Hetero   | 14     | 29        | 1.2 (0.4–3.2) |
| ICAM5       | rs281438  | Vitamin use | Variant  | 4      | 3         | 3.3 (0.6–17.6) |
| ICAM5       | rs281438  | No vitamin use | Wildtype | 4      | 22        | Reference    |
| ICAM5       | rs281438  | No vitamin use | Hetero   | 11     | 5         | 12.1 (2.7–54.3)** |
| ICAM5       | rs281440  | Vitamin use | Wildtype | 2      | 30        | Reference    |
| ICAM5       | rs281440  | Vitamin use | Hetero   | 20     | 25        | 12.0 (2.6–56.4) |
| ICAM5       | rs281440  | Vitamin use | Variant  | 3      | 4         | 11.2 (1.4–89.2) |

(Continued)
| Gene Symbol | dbSNP ID  | Subgroup         | Genotype  | Case N | Control N | OR (95% CI) |
|-------------|-----------|------------------|-----------|--------|-----------|-------------|
| ICAM5       | rs281440  | No vitamin use   | Wildtype  | 0      | 18        | Reference   |
| ICAM5       | rs281440  | No vitamin use   | Hetero    | 15     | 15        | NC          |
| ICAM5       | rs281440  | No vitamin use   | Variant   | 1      | 2         | NC          |
| ICAM5       | rs2075741 | Vitamin use      | Wildtype  | 11     | 23        | Reference   |
| ICAM5       | rs2075741 | Vitamin use      | Hetero    | 11     | 25        | 0.9 (0.3–2.5) |
| ICAM5       | rs2075741 | Vitamin use      | Variant   | 10     | 17        | 1.2 (0.4–3.6) |
| ICAM5       | rs2075741 | No vitamin use   | Wildtype  | 6      | 18        | Reference   |
| ICAM5       | rs2075741 | No vitamin use   | Hetero    | 9      | 11        | 2.5 (0.7–8.8) |
| ICAM5       | rs2075741 | No vitamin use   | Variant   | 12     | 7         | 5.1 (1.4–19.1) |
| NOS3        | rs1036145 | Smoking          | Wildtype  | 6      | 8         | Reference   |
| NOS3        | rs1036145 | Smoking          | Hetero    | 3      | 7         | 0.6 (0.1–3.2) |
| NOS3        | rs1036145 | Smoking          | Variant   | 2      | 0         | NC          |
| NOS3        | rs1036145 | No Smoking       | Wildtype  | 33     | 39        | Reference   |
| NOS3        | rs1036145 | No Smoking       | Hetero    | 10     | 42        | 0.3 (0.1–0.6) |
| NOS3        | rs1036145 | No Smoking       | Variant   | 6      | 6         | 1.2 (0.3–4.0) |
| NOS3        | rs10277237| Smoking          | Wildtype  | 4      | 3         | 2.2 (0.3–16.4) |
| NOS3        | rs10277237| Smoking          | Hetero    | 3      | 3         | NC          |
| NOS3        | rs10277237| No Smoking       | Wildtype  | 11     | 29        | Reference   |
| NOS3        | rs10277237| No Smoking       | Hetero    | 15     | 37        | 1.1 (0.4–2.7) |
| NOS3        | rs10277237| No Smoking       | Variant   | 16     | 11        | 3.8 (1.4–10.8) |
| NPPA        | rs5065    | Smoking          | Wildtype  | 9      | 13        | Reference   |
| NPPA        | rs5065    | Smoking          | Hetero    | 3      | 2         | NC          |
| NPPA        | rs5065    | Smoking          | Variant   | 0      | 0         | NC          |
| NPPA        | rs5065    | No Smoking       | Wildtype  | 42     | 67        | Reference   |
| NPPA        | rs5065    | No Smoking       | Hetero    | 5      | 22        | 0.4 (0.1–1.0) |
| NPPA        | rs5065    | No Smoking       | Variant   | 1      | 0         | NC          |
| ADD1        | rs7678161 | Smoking          | Wildtype  | 3      | 6         | Reference   |
| ADD1        | rs7678161 | Smoking          | Hetero    | 7      | 7         | 2.0 (0.4–11.4) |
| ADD1        | rs7678161 | Smoking          | Variant   | 0      | 0         | NC          |
| ADD1        | rs7678161 | No Smoking       | Wildtype  | 22     | 31        | Reference   |
| ADD1        | rs7678161 | No Smoking       | Hetero    | 12     | 41        | 0.4 (0.2–1.0) |
| ADD1        | rs7678161 | No Smoking       | Variant   | 2      | 2         | NC          |
| ADD1        | rs12503220| Smoking          | Wildtype  | 7      | 12        | Reference   |
| ADD1        | rs12503220| Smoking          | Hetero    | 5      | 3         | 2.9 (0.5–15.8) |
| ADD1        | rs12503220| Smoking          | Variant   | 0      | 0         | NC          |
| ADD1        | rs12503220| No Smoking       | Wildtype  | 24     | 66        | Reference   |
| ADD1        | rs12503220| No Smoking       | Hetero    | 22     | 18        | 3.4 (1.5–7.3) |
| ADD1        | rs12503220| No Smoking       | Variant   | 4      | 6         | 1.8 (0.5–7.1) |
| GNB3        | Rs5443    | Smoking          | Wildtype  | 9      | 7         | Reference   |
| GNB3        | Rs5443    | Smoking          | Hetero    | 2      | 5         | NC          |
| GNB3        | Rs5443    | Smoking          | Variant   | 1      | 3         | NC          |
| GNB3        | Rs5443    | No Smoking       | Wildtype  | 34     | 36        | Reference   |
| GNB3        | Rs5443    | No Smoking       | Hetero    | 8      | 38        | 0.2 (0.1–0.5) |
| GNB3        | Rs5443    | No Smoking       | Variant   | 6      | 12        | 0.5 (0.2–1.6) |
| ICAM5       | rs281417  | Smoking          | Wildtype  | 2      | 7         | Reference   |
| ICAM5       | rs281417  | Smoking          | Hetero    | 4      | 4         | NC          |
| ICAM5       | rs281417  | Smoking          | Variant   | 2      | 2         | NC          |
| ICAM5       | rs281417  | No Smoking       | Wildtype  | 11     | 37        | Reference   |
| ICAM5       | rs281417  | No Smoking       | Hetero    | 21     | 30        | 2.4 (1.0–5.6) |
| ICAM5       | rs281417  | No Smoking       | Variant   | 5      | 3         | 5.6 (1.2–27.3) |
| ICAM5       | rs281440  | Smoking          | Wildtype  | 0      | 6         | Reference   |
| ICAM5       | rs281440  | Smoking          | Hetero    | 5      | 5         | NC          |
| ICAM5       | rs281440  | Smoking          | Variant   | 1      | 1         | NC          |
| ICAM5       | rs281440  | No Smoking       | Wildtype  | 1      | 41        | Reference   |
| ICAM5       | rs281440  | No Smoking       | Hetero    | 30     | 35        | NC          |
| ICAM5       | rs281440  | No Smoking       | Variant   | 3      | 5         | NC          |
| Gene symbol | Haplotype | Frequency | Case, control ratio counts | OR (95% CI) |
|-------------|-----------|-----------|----------------------------|-------------|
| All race/ethnicities | | | | |
| ADD1 | TG | 0.52 | 81.8:76.2, 156.1:141.9 | 1.0 (0.7–1.4) |
| ADD1 | CG | 0.29 | 46.7:111.3, 86.0:212.0 | 1.0 (0.7–1.6) |
| ADD1 | CA | 0.18 | 28.3:129.7, 55.7:242.3 | 0.9 (0.6–1.6) |
| ADD1 | TA | 0.003 | 1.2:156.8, 0.2:297.8 | NC |
| ICAM1 | TCA | 0.44 | 71.7:84.3, 125.8:168.2 | 1.1 (0.8–1.7) |
| ICAM1 | TTG | 0.28 | 52.2:103.8, 74.9:219.1 | 1.5 (1.0–2.2) |
| ICAM1 | ATG | 0.14 | 17.2:138.8, 45.7:248.3 | 0.7 (0.4–1.2) |
| ICAM1 | TCG | 0.136 | 13.8:142.2, 47.3:246.7 | 0.5 (0.3–1.0) |
| ICAM1 | ACA | 0.003 | 1.1:154.9, 0.2:295.8 | NC |
| TNF | CG | 0.69 | 112.0:42.0, 198.0:96.0 | 1.3 (0.8–2.0) |
| TNF | AG | 0.228 | 31.0:123.0, 71.0:223.0 | 0.8 (0.5–1.3) |
| TNF | AA | 0.08 | 11.0:143.0, 25.0:269.0 | 0.8 (0.4–1.7) |
| NOS3 | GC | 0.765 | 118.9:35.1, 223.8:70.2 | 1.1 (0.7–1.7) |
| NOS3 | CT | 0.229 | 34.9:119.1, 67.7:229.3 | 1.0 (0.6–1.6) |
| NOS3 | CC | 0.003 | 0.1:153.9, 0.2:293.8 | NC |
| NOS3 | GT | 0.003 | 0.1:153.9, 0.2:293.8 | NC |
| White | | | | |
| ICAM1 | TCA | 0.489 | 32.2:27.8, 48.0:56.0 | 1.4 (0.7–2.6) |
| ICAM1 | TTG | 0.198 | 14.5:45.5, 18.0:86.0 | 1.5 (0.7–3.3) |
| ICAM1 | ATG | 0.17 | 8.0:52.0, 20.0:84.0 | 0.6 (0.3–1.6) |
| ICAM1 | TCG | 0.14 | 5.3:34.7, 18.0:86.0 | 0.5 (0.2–1.3) |
| NPPA | GA | 0.854 | 53.0:70.0, 87.0:210.0 | 1.5 (0.6–3.8) |
| NPPA | AG | 0.11 | 7.0:53.0, 11.0:93.0 | 1.1 (0.4–3.1) |
| NPPA | GG | 0.03? | 0.0:60.0, 0.0:96.0 | NC |
| NOS3 | GC | 0.705 | 44.0:14.0, 68.9:33.1 | 1.5 (0.7–3.1) |
| NOS3 | CT | 0.279 | 14.0:44.0, 30.7:71.3 | 0.7 (0.4–1.5) |
| NOS3 | CC | 0.008 | 0.0:58.0, 1.3:100.7 | NC |
| NOS3 | GT | 0.003 | 0.0:58.0, 1.2:100.8 | NC |
| Native-born Hispanic | | | | |
| ICAM1 | TG | 0.44 | 16.8:23.2, 23.8:28.2 | 0.9 (0.4–2.0) |
| ICAM1 | CA | 0.41 | 17.0:23.0, 21.0:31.0 | 1.1 (0.5–2.5) |
| ICAM1 | CG | 0.14? | 6.2:33.8, 7.2:44.8 | 1.1 (0.4–3.7) |
| ICAM5 | CC | 0.510 | 21.0:21.0, 28.0:26.0 | 0.9 (0.4–2.1) |
| ICAM5 | GT | 0.408 | 18.7:23.3, 20.5:33.5 | 1.3 (0.6–3.0) |
| ICAM5 | CT | 0.082 | 2.3:39.7, 5.5:48.5 | 0.5 (0.2–1.5) |
| NOS3 | GC | 0.702 | 28.0:14.0, 38.0:14.0 | 0.7 (0.3–1.8) |
| NOS3 | CT | 0.298 | 14.0:28.0, 14.0:38.0 | 1.4 (0.6–3.3) |
| NOS3 | GA | 0.696 | 26.9:15.1, 39.9:14.1 | 0.6 (0.3–1.5) |
| NOS3 | TG | 0.270 | 13.9:28.1, 12.0:42.0 | 1.7 (0.7–4.3) |
| NOS3 | TA | 0.022 | 0.1:41.9, 2.1:51.9 | 0.1 (0.0–3.9) |
| NOS3 | GG | 0.011 | 1.1:40.9, 0.0:54.0 | NC |
| Foreign-born Hispanic | | | | |
| ICAM1 | TG | 0.499 | 21.8:16.2, 39.0:45.0 | 1.6 (0.7–3.4) |
| ICAM1 | CA | 0.392 | 14.8:32.2, 33.0:51.0 | 1.0 (0.4–2.2) |
| ICAM1 | CG | 0.110 | 1.4:36.6, 12.0:21.0 | 0.2 (0.0–1.4) |
| NOS3 | GC | 0.844 | 32.0:4.0, 71.0:15.0 | 1.7 (0.5–5.5) |
| NOS3 | CT | 0.156 | 4.0:32.0, 15.0:71.0 | 0.6 (0.2–1.9) |

All race/ethnicities: ADD1 included rs3775068, rs10026792; ICAM1 included rs1059840, rs11115, rs1059849; TNF included rs1041981, rs1800629; NOS3 included rs2373962, rs6951150.

White: ICAM1 included rs1059840, rs11115, rs1059849; NPPA included rs198372, rs198373; NOS3 included rs2373962, rs6951150.

Native-born Hispanic: ICAM1 included rs11115, rs1059849, ICAM5 included rs2075741, rs2569702; NOS3 included rs2373962, rs6951150, rs4496877, rs1800779.

Foreign-born Hispanic: ICAM1 included rs11115, rs1059849; NOS3 included rs2373962, rs6951150.

NC is not calculated because one of the case, control ratio counts is 0.

ORs are not calculated where the estimate in the frequency is <0.01.
In a previous California study of selected births between 1988–1990, which investigated many of the same genes and variants, Torfs et al. [2006] found the following gene variants associated with increased risk for gastroschisis: heterozygotes in ICAM1 (rs1799969), NOS3 (rs1799983), NPPA (rs5065), and ADD1 (rs4961). Additionally, for NPPA and ADD1, homozygote variants were associated with higher risk than the heterozygotes [Torfs et al., 2006]. The results of the specific variants were not confirmed by the current study; however, the both studies found associations with the same patho-genetic groupings.

In the current study, tests of effect modification revealed interactions between folic acid-containing vitamin use and several ICAM and ADD1 gene variants in infants indicating a protective effect of vitamin use in the context of these variants. Conversely, SCNN1A, MTHFR, ADD1, and AGT variants were associated with either decreased risk with no vitamin use or increased risk with vitamin use. When stratified by age groups, four NOS3 gene variants were associated with gastroschisis among women aged 20–24. ADD1 variants were associated with gastroschisis among women over 25. None of the investigated gene variants seemed to be associated with greater frequency among gastroschisis infants whose mothers were teenagers.

We did not identify an interaction among women who smoked during the peri-conceptional period, but the study population had too few smokers to adequately estimate possible effect modification. We did find a decreased risk of gastroschisis among non-smokers with variants of NPPA and ADD1. A previous study a decade earlier in the same geographic area, found interactions between maternal smoking and NOS3, ICAM1, and NPPA [Torfs et al., 2006]. These inconsistent results may be attributable to a decrease in the smoking rate among pregnant mothers between 1988–1990 and 1997–2001 [Torfs et al., 2006].

Among genes with variants we showed to be associated with gastroschisis, those related to blood pressure may be potential candidates for future studies owing to the hypothesis that this phenotype has an underlying pathogenesis associated with vascular disruption [Feldkamp et al., 2007]. Previous studies corroborate the biologic mechanism by which NOS3 and ADD1 may be associated with gastroschisis. The NOS3 gene has been hypothesized to be associated with gastroschisis [Lammer et al., 2008]. When NOS3 is activated, it translocates into the cytosol, where it can convert arginine to nitric oxide (NO), which plays important physiological roles as a mediator of vascular tone. NOS3 also contributes crucial roles in regulating endothelial migration, angiogenesis, and vascular remodeling [Murohara et al., 1998; Rudic et al., 1998; Aicher et al., 2003; Ahmad et al., 2006]. NO seems to function as a maintenance factor for several integrins that are important regulators of cell migration and angiogenesis [Murohara et al., 1999; Lee et al., 2000]. These processes are likely important to the development of gastroschisis, whose pathogenesis may be linked to vascular disruption—but the pathogenesis remains uncertain, in part because of the absence of spontaneously occurring gastroschisis among experimental animal models, like mice. Additionally, ADD1 is important in epidermal differentiation, cell proliferation and wound repair [Guo et al., 2005].

ICAM is another gene that has been hypothesized to be associated with gastroschisis and is related to cell–cell interaction. ICAM1 is linked to nitric oxide production and control over vascular remodeling. Cell adhesion molecules are important for the coordinated regulation of endothelial cell migration during angiogenesis. ICAMs are a family of cell surface proteins including a subset that is encoded by three genes (ICAM1, 4–5) clustered at chromosome 19p32 [Hayflick et al., 1998]. Each ICAM binds a LFA-1 ligand and perhaps other ligands, providing essential adhesion signals. Recent experiments have shown that endothelial cell adhesion molecules are likely to be involved in angiogenesis [Lammer et al., 2008].

Our study has several strengths including its population-based design, complete case ascertainment by a well-established active birth defects monitoring program and detailed information on critical covariates such as vitamin use and exposure to active and passive cigarette smoke. We investigated a large number of gene variants involved in several biologically relevant pathways, that is, homocysteine metabolism, blood pressure regulation, coagulation, cell–cell interaction, and inflammatory response. Notably, we were able to evaluate genetic risks of gastroschisis in combination with important covariates including age, race/ethnicity, vitamin use and smoking, and risk of gastroschisis. Given the relatively recent increase in gastroschisis (decades), it does not seem likely that gastroschisis would have a sole genetic etiology, but rather an etiology explained by gene-environment interaction.

Our results need to be considered relative to some limitations as well. Sample sizes for many comparisons were modest contributing to imprecision in potential risk estimation. Our study was limited to the infant genotype information. Thus, we were unable to investigate the effect of the maternal genotype. As with any study that seeks to explore associations with a large number of genotypes, findings are subject to chance owing to multiple comparisons. Further, the selected gene variants represent only a fraction of the potential variation of the studied genes.

Our study rigorously adds to the scant literature on this topic and provides further information on candidate genes for future studies. Specifically, NOS3, ADD1, and ICAM warrant further investigation in additional populations, ideally larger, and with the interaction of additional environmental exposures.

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