ORIGINAL ARTICLE

AMERICAN JOURNAL OF medical genetics PART A

Gene Variants as Risk Factors for Gastroschisis

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Manuscript Received: 30 March 2016; Manuscript Accepted: 27 July 2016

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. We found 11 gene variants with increased risk and four variants with decreased risk of gastroschisis for heterozygous (OR_h) or homozygous variants (OR_v) genotypes. These included *NOS3* (rs1036145) $OR_h = 0.4$ (95% CI: 0.2–0.7); *NOS3* (rs10277237) $OR_v = 2.7$ (95% CI: 1.3–6.0); *ADD1* (rs12503220) $OR_h = 2.9$ (95% CI: 1.6–5.4), GNB3 (rs5443) $OR_h = 0.2$ (95% CI: 0.1–0.5), $OR_v = 0.4$ (95% CI: 0.2–0.9); *ICAM1* (rs281428) $OR_v = 6.9$ (95% CI: 2.1–22.9), *ICAM1* (rs3093030) $OR_v = 2.6$ (95% CI: 1.2–5.6); *ICAM4* (rs281438) $OR_v = 4.9$ (95% CI: 1.4–16.6), *ICAM5* (rs281417) $OR_h = 2.1$ (95% CI: 1.1–4.1), $OR_v = 4.8$ (95% CI: 1.7–13.6); *ICAM5* (rs281440) $OR_h = 23.7$ (95% CI: 5.5–102.5), $OR_v = 20.6$ (95% CI: 3.4–124.3); *ICAM5* (rs2075741) $OR_v = 2.2$ (95% CI: 1.1–4.4); *NAT1* $OR_v = 0.3$ (95% CI: 0.1–0.9). There were additional associations between several gene variants and gastroschisis among women aged 20–24 and among mothers with and without vitamin use. *NOS3*, *ADD1*, *ICAM1*, *ICAM4*, and *ICAM5* warrant further investigation in additional populations and with the interaction of additional environmental exposures.

Key words: gastroschisis; gene variant

How to Cite this Article:
Padula AM, Yang W, Schultz K, Tom L, Lin B, Carmichael SL, Lammer EJ, Shaw GM. 2016. Gene variants as risk factors for gastroschisis.
Am J Med Genet Part A 170A:2788–2802.

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].

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.

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

Grant sponsor: Centers for Disease Control and Prevention; Grant number: U50/CCU913241; Grant sponsor: California Tobacco-Related Disease Research Program; Grant number: 16RT-0086; Grant sponsor: NIH; Grant numbers: R00ES021470, K99ES021470, L40ES023163.

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Article first published online in Wiley Online Library (wileyonlinelibrary.com): 12 September 2016
DOI 10.1002/ajmg.a.37883

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 consitituents, *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 Haploview) 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 periconceptional 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 (OR_h) and homozygous (OR_v) variants. These included *NOS3* (rs1036145) $OR_h = 0.4$ (95% CI: 0.2–0.7); *NOS3* (rs10277237) $OR_v = 2.7$ (95% CI: 1.3–6.0); *ADD1* (rs12503220) $OR_h = 2.9$ (95% CI: 1.6–5.4), *GNB3* (rs5443) $OR_h = 0.2$ (95% CI: 0.1–0.5), $OR_v = 0.4$ (95% CI: 0.2–0.9); *ICAM1* (rs281428) $OR_v = 6.9$ (95% CI: 2.1–22.9), *ICAM1* (rs3093030) $OR_v = 2.6$ (95% CI: 1.2–5.6); *ICAM4* (rs281438) $OR_v = 4.9$ (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)		Interviewed participants (n = 169)	
	Cases[a] (n = 79)	Controls[a] (n = 149)	Cases[a] (n = 63)	Controls[a] (n = 106)
Maternal race/ethnicity				
White	30 (38.0)	52 (34.9)	21 (33.3)	43 (40.6)
U.S.-born Hispanic	21 (26.6)	27 (18.1)	19 (30.2)	19 (17.9)
Foreign-born Hispanic	19 (24.1)	43 (28.9)	15 (23.8)	34 (32.1)
Other	9 (11.4)	23 (15.4)	8 (12.7)	8 (7.5)
Maternal age at delivery (years)				
<20	36 (45.6)	22 (14.8)	30 (47.6)	13 (12.3)
20–24	26 (32.9)	42 (28.2)	19 (30.2)	31 (29.2)
>25	17 (21.5)	81 (54.4)	14 (22.2)	60 (56.6)
Maternal education (years)				
<12	38 (48.1)	45 (30.2)	28 (44.4)	31 (29.2)
12	28 (35.4)	56 (37.6)	25 (39.7)	37 (34.9)
>12	11 (13.9)	42 (28.2)	9 (14.3)	36 (34.0)
Parity				
0	53 (67.1)	44 (29.5)	44 (69.8)	34 (32.1)
1+	26 (32.9)	101 (67.8)	19 (30.2)	70 (66.0)
Plurality				
Singletons	79 (100.0)	143 (96.0)	63 (100.0)	103 (97.2)
Infant sex				
Male	45 (57.0)	74 (49.7)	34 (54.0)	52 (49.1)
Female	34 (43.0)	71 (47.7)	29 (46.0)	52 (49.1)
Multi-vitamin Use[b]				
No	N/A	N/A	27 (42.9)	37 (34.9)
Yes	N/A	N/A	35 (55.6)	69 (65.1)
Smoking[b]				
None	N/A	N/A	50 (79.4)	90 (84.9)
Any	N/A	N/A	12 (19.0)	15 (14.2)

N/A not applicable because interview was not conducted.
[a]Percentages may not equal 100 owing to rounding and missing.
[b]During the month before or the first 2 months of pregnancy.

TABLE II. Characteristics of Gene Variants Among All Racial/Ethnic Groups, California 1997–2001, HWE Evaluated Using HaploView Program

Gene Symbol	dbSNP ID	Position	Reference Allele[a]	Call rate %	MAF[b]	HWE P[b]
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	0.23	0.185
NOS3	rs6951150	150119562	C	78.9	0.22	0.031
NOS3	rs10277237	150120992	G	83.8	0.38	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	151005693	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	0.176
ADD1	rs735794	2809236	C	90.4	0.47	0.262
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	2888441	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	2915080	C	92.5	0.17	0.139
ADD1	rs1263359	2925576	C	97.4	0.43	0.057
ADD1	rs3775067	2925628	C	93.4	0.48	0.011
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	148826877	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	100776931	G	97.8	0.36	0.302
FGB	rs1799768	100785547	G	97.8	0.17	0.323
SERPINE1	rs1799889	101126430	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	169726729	C	98.2	0.04	1.000

(*Continued*)

TABLE II. (*Continued*)

Gene Symbol	dbSNP ID	Position	Reference Allele[a]	Call rate %	MAF[b]	HWE P[b]
SELE	rs5361	169731919	A	98.2	0.05	0.063
ICAM1	rs1059840	10231490	A	95.2	0.15	0.431
ICAM1	rs11115	10231542	C	96.5	0.41	0.193
ICAM1	rs1059849	10231654	A	97.8	0.43	0.221
ICAM1	rs281428	10249324	T	99.6	0.23	0.101
ICAM5	rs2075741	10258238	C	96.1	0.44	0.003
ICAM5	rs2569702	10264947	T	100	0.50	0.151
ICAM5	rs2291473	10276781	C	95.2	0.09	0.561
ICAM5	rs281419	10277842	G	99.1	0.14	<0.001
ICAM1	rs281432	10279982	C	94.3	0.43	0.643
ICAM5	rs281417	10280130	T	80.7	0.26	0.946
ICAM1	rs1799969	10284116	G	97.4	0.15	0.033
ICAM1	rs3093030	10286727	C	79.8	0.28	<0.001
ICAM5	rs281439	10289434	C	92.5	0.22	<0.001
ICAM1	rs5030390	10382537	A	100	0.03	1.000
ICAM1	rs3093032	10396335	C	80.7	0.08	1.000
ICAM4	rs281438	10399375	G	97.8	0.15	0.829
ICAM5	rs281440	10400304	A	78.5	0.28	0.499
ICAM5	rs2228615	10403368	A	92.1	0.49	0.041
ICAM5	rs892188	10409793	C	95.2	0.41	<0.001
Inflammatory response						
LTA	rs1041981	31573007	C	98.2	0.33	0.464
TNF	rs1800629	31575254	G	98.2	0.09	1.000
TNF	rs361525	31575324	G	96.1	0.05	0.496
MMP3	rs35068180	2845216	A	97.8	0.36	0.752
GSTT1	rs1234	1234	Absent	99.6	0.17	NA
GSTM1	rs5678	5678	Absent	99.6	0.37	NA
NAT1		1088	T	98.2	0.38	0.078

NA not applicable (patterns are absent/present and HWE *P*-value is not available).
[a]Determined by most frequent allele among controls.
[b]Among controls (N = 149).

(rs281417) $OR_h = 2.1$ (95% CI: 1.1–4.1), $OR_v = 4.8$ (95% CI: 1.7–13.6); *ICAM5* (rs2075741) $OR_v = 2.2$ (95% CI: 1.1–4.4); *NAT1* $OR_v = 0.3$ (95% CI: 0.1–0.9).

Results of gene variant analyses stratified by maternal race/ethnicity, age at delivery, vitamin use and smoking in early pregnancy are shown in Table III. No statistically significant differences were observed between gene variants and risk of gastroschisis among the various race/ethnic groups. We observed gene variant risks of gastroschisis that differed between these subgroups. Among women aged 20–24, there were increased risks of gastroschisis associated with the following heterozygous gene variants: *NOS3* (rs1800779), *NOS3* (rs2373962), *NOS3* (rs4496877), and *NOS3* (rs6951150). Among women aged 25+ homozygous variants of ADD1 (rs2285084) were associated with increased risk of gastroschisis.

The following gene variants were associated with increased risk of gastroschisis among mothers with no vitamin use: *ADD1* (rs10026792), *ICAM4* (rs281438), *ICAM5* (rs281417) and a decreased risk among mothers with vitamin use: *ADD1* (rs7678161), *ICAM1* (rs281432). There were also some results in the unexpected direction. Heterozygous variants of *MTHFR* (rs1801133) and *AGT* (rs699) were associated with increased risk among vitamin users and *SCNN1A* (rs2228576) was associated with decreased risk among non-vitamin users.

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)
			Race/ethnicity			
MTHFR	rs1801133	White NH	Wildtype	10	20	Reference
MTHFR	rs1801133	White NH	Hetero	16	27	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	NC
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	NC
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	NC
NOS3	rs3918188	FB Hispanic	Wildtype	5	25	Reference
NOS3	rs3918188	FB Hispanic	Hetero	11	17	**3.2 (1.0–11.0)**
NOS3	rs3918188	FB Hispanic	Variant	3	1	NC
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	NC
ADD1	rs12503220	NB Hispanic	Wildtype	7	17	Reference
ADD1	rs12503220	NB Hispanic	Hetero	12	7	**4.2 (1.2–15.0)**
ADD1	rs12503220	NB Hispanic	Variant	2	2	NC
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	NC
GNB3	Rs5443	NB Hispanic	Wildtype	14	9	Reference
GNB3	Rs5443	NB Hispanic	Hetero	4	13	**0.2 (0.0–0.8)**
GNB3	Rs5443	NB Hispanic	Variant	2	3	NC
GNB3	Rs5443	FB Hispanic	Wildtype	13	17	Reference
GNB3	Rs5443	FB Hispanic	Hetero	4	15	0.3 (0.1–1.3)
GNB3	Rs5443	FB Hispanic	Variant	2	10	NC

(*Continued*)

TABLE III. (*Continued*)

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	Reference
SERPINE1	rs1799889	NB Hispanic	Hetero	9	10	1.1 (0.3–3.7)
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	**4.4 (1.2–16.2)**
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
SELE	rs5361	FB Hispanic	Variant	0	0	NC
ICAM1	rs11115	White NH	Wildtype	12	24	Reference
ICAM1	rs11115	White NH	Hetero	12	18	1.3 (0.5–3.6)
ICAM1	rs11115	White NH	Variant	5	10	1.0 (0.3–3.6)
ICAM1	rs11115	NB Hispanic	Wildtype	6	7	Reference
ICAM1	rs11115	NB Hispanic	Hetero	10	13	NC
ICAM1	rs11115	NB Hispanic	Variant	3	5	NC
ICAM1	rs11115	FB Hispanic	Wildtype	1	14	Reference
ICAM1	rs11115	FB Hispanic	Hetero	13	17	NC
ICAM1	rs11115	FB Hispanic	Variant	4	11	NC
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	7	NC
ICAM1	rs3093030	FB Hispanic	Variant	3	2	NC
ICAM5	rs281440	White NH	Wildtype	2	22	Reference
ICAM5	rs281440	White NH	Hetero	14	19	**8.1 (1.6–40.3)**
ICAM5	rs281440	White NH	Variant	3	4	**8.2 (1.0–66.2)**
ICAM5	rs281440	NB Hispanic	Wildtype	0	11	Reference
ICAM5	rs281440	NB Hispanic	Hetero	13	9	NC
ICAM5	rs281440	NB Hispanic	Variant	0	0	NC
ICAM5	rs281440	FB Hispanic	Wildtype	0	18	Reference
ICAM5	rs281440	FB Hispanic	Hetero	11	22	NC
ICAM5	rs281440	FB Hispanic	Variant	1	1	NC
ICAM5	rs2075741	White NH	Wildtype	6	13	Reference
ICAM5	rs2075741	White NH	Hetero	8	23	0.8 (0.2–2.7)
ICAM5	rs2075741	White NH	Variant	15	16	2.0 (0.6–6.7)
ICAM5	rs2075741	NB Hispanic	Wildtype	7	13	Reference
ICAM5	rs2075741	NB Hispanic	Hetero	9	6	2.8 (0.7–11.1)
ICAM5	rs2075741	NB Hispanic	Variant	4	6	1.2 (0.3–5.9)
ICAM5	rs2075741	FB Hispanic	Wildtype	6	23	Reference
ICAM5	rs2075741	FB Hispanic	Hetero	6	14	1.6 (0.4–6.1)
ICAM5	rs2075741	FB Hispanic	Variant	5	4	**4.8 (1.0–23.6)**
ICAM5	rs2569702	White NH	Wildtype	16	16	Reference
ICAM5	rs2569702	White NH	Hetero	10	28	**0.4 (0.1–1.0)**
ICAM5	rs2569702	White NH	Variant	4	8	0.5 (0.1–2.0)
ICAM5	rs2569702	NB Hispanic	Wildtype	5	8	Reference
ICAM5	rs2569702	NB Hispanic	Hetero	11	10	1.8 (0.4–7.2)

(*Continued*)

TABLE III. (*Continued*)

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)
			Age			
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	rs1800779	Age 25+	Wildtype	11	45	Reference
NOS3	rs1800779	Age 25+	Hetero	5	29	0.7 (0.2–2.2)
NOS3	rs1800779	Age 25+	Variant	1	6	NC
NOS3	rs2373962	Age <20	Wildtype	25	13	Reference
NOS3	rs2373962	Age <20	Hetero	11	7	0.8 (0.3–2.6)
NOS3	rs2373962	Age <20	Variant	0	2	NC
NOS3	rs2373962	Age 20–24	Wildtype	10	32	Reference
NOS3	rs2373962	Age 20–24	Hetero	10	7	**4.6 (1.4–15.2)****
NOS3	rs2373962	Age 20–24	Variant	4	2	NC
NOS3	rs2373962	Age 25+	Wildtype	12	42	Reference
NOS3	rs2373962	Age 25+	Hetero	3	29	0.4 (0.1–1.4)
NOS3	rs2373962	Age 25+	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 20–24	Variant	4	4	1.5 (0.3–6.9)
NOS3	rs3918188	Age 25+	Wildtype	5	43	Reference
NOS3	rs3918188	Age 25+	Hetero	7	32	1.9 (0.5–6.5)
NOS3	rs3918188	Age 25+	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 20–24	Variant	3	1	NC
NOS3	rs4496877	Age 25+	Wildtype	12	40	Reference
NOS3	rs4496877	Age 25+	Hetero	4	35	0.4 (0.1–1.3)
NOS3	rs4496877	Age 25+	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*)

TABLE III. (*Continued*)

Gene Symbol	dbSNP ID	Subgroup	Genotype	Case N	Control N	OR (95% CI)
NOS3	rs6951150	Age 25+	Variant	1	6	NC
ADD1	rs2285084	Age <20	Wildtype	26	13	Reference
ADD1	rs2285084	Age <20	Hetero	8	7	0.6 (0.2–1.9)
ADD1	rs2285084	Age <20	Variant	2	2	NC
ADD1	rs2285084	Age 20–24	Wildtype	17	29	Reference
ADD1	rs2285084	Age 20–24	Hetero	8	8	1.7 (0.5–5.4)
ADD1	rs2285084	Age 20–24	Variant	1	5	NC
ADD1	rs2285084	Age 25+	Wildtype	6	51	Reference
ADD1	rs2285084	Age 25+	Hetero	8	26	2.6 (0.8–8.3)
ADD1	rs2285084	Age 25+	Variant	3	4	**6.4 (1.1–35.6)***
ADD1	rs7678161	Age <20	Wildtype	13	11	Reference
ADD1	rs7678161	Age <20	Hetero	11	8	1.2 (0.3–3.9)
ADD1	rs7678161	Age <20	Variant	1	2	NC
ADD1	rs7678161	Age 20–24	Wildtype	6	16	Reference
ADD1	rs7678161	Age 20–24	Hetero	8	17	1.3 (0.4–4.4)
ADD1	rs7678161	Age 20–24	Variant	1	1	NC
ADD1	rs7678161	Age 25+	Wildtype	10	23	Reference
ADD1	rs7678161	Age 25+	Hetero	5	42	**0.3 (0.1–0.9)**
ADD1	rs7678161	Age 25+	Variant	0	2	NC
ADD1	rs12503220	Age <20	Wildtype	20	14	Reference
ADD1	rs12503220	Age <20	Hetero	12	5	1.7 (0.5–5.8)
ADD1	rs12503220	Age <20	Variant	4	3	0.9 (0.2–4.8)
ADD1	rs12503220	Age 20–24	Wildtype	12	29	Reference
ADD1	rs12503220	Age 20–24	Hetero	14	7	**4.8 (1.6–15.0)**
ADD1	rs12503220	Age 20–24	Variant	0	5	NC
ADD1	rs12503220	Age 25+	Wildtype	9	63	Reference
ADD1	rs12503220	Age 25+	Hetero	6	15	2.8 (0.9–9.1)
ADD1	rs12503220	Age 25+	Variant	2	3	NC
ADD1	rs16843523	Age <20	Wildtype	25	13	Reference
ADD1	rs16843523	Age <20	Hetero	7	6	0.6 (0.2–2.2)
ADD1	rs16843523	Age <20	Variant	3	2	NC
ADD1	rs16843523	Age 20–24	Wildtype	17	29	Reference
ADD1	rs16843523	Age 20–24	Hetero	6	8	1.3 (0.4–4.3)
ADD1	rs16843523	Age 20–24	Variant	3	2	NC
ADD1	rs16843523	Age 25+	Wildtype	8	50	Reference
ADD1	rs16843523	Age 25+	Hetero	3	19	1.0 (0.2–4.1)
ADD1	rs16843523	Age 25+	Variant	3	3	**6.3 (1.1–36.5)**
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	Reference
GNB3	rs5443	Age 20–24	Hetero	3	17	**0.2 (0.0–0.7)**
GNB3	rs5443	Age 20–24	Variant	4	7	0.5 (0.1–2.2)
GNB3	rs5443	Age 25+	Wildtype	11	32	Reference
GNB3	rs5443	Age 25+	Hetero	4	34	0.3 (0.1–1.2)
GNB3	rs5443	Age 25+	Variant	2	11	NC
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	NC
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	NC
ADRB2	rs1042714	Age 25+	Wildtype	14	58	Reference
ADRB2	rs1042714	Age 25+	Hetero	2	16	NC
ADRB2	rs1042714	Age 25+	Variant	0	5	NC
ICAM1	rs281432	Age <20	Wildtype	13	7	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*)

TABLE III. (*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	rs281432	Age 25+	Hetero	4	41	**0.2 (0.1–0.9)**
ICAM1	rs281432	Age 25+	Variant	3	14	0.5 (0.1–2.3)
ICAM1	rs1059849	Age <20	Wildtype	13	5	Reference
ICAM1	rs1059849	Age <20	Hetero	13	9	0.6 (0.1–2.1)
ICAM1	rs1059849	Age <20	Variant	8	8	0.4 (0.1–1.6)
ICAM1	rs1059849	Age 20–24	Wildtype	9	14	Reference
ICAM1	rs1059849	Age 20–24	Hetero	10	16	1.0 (0.3–3.1)
ICAM1	rs1059849	Age 20–24	Variant	7	12	0.9 (0.3–3.2)
ICAM1	rs1059849	Age 25+	Wildtype	3	31	Reference
ICAM1	rs1059849	Age 25+	Hetero	8	37	2.2 (0.5–9.2)
ICAM1	rs1059849	Age 25+	Variant	5	11	**4.7 (1.0–23.0)**
ICAM5	rs281440	Age <20	Wildtype	1	13	Reference
ICAM5	rs281440	Age <20	Hetero	17	6	NC
ICAM5	rs281440	Age <20	Variant	3	1	NC
ICAM5	rs281440	Age 20–24	Wildtype	1	11	Reference
ICAM5	rs281440	Age 20–24	Hetero	16	20	NC
ICAM5	rs281440	Age 20–24	Variant	0	3	NC
ICAM5	rs281440	Age 25+	Wildtype	0	39	Reference
ICAM5	rs281440	Age 25+	Hetero	8	31	NC
ICAM5	rs281440	Age 25+	Variant	2	3	NC
GSTT1 & GSTM1		Age <20	No Null	17	8	Reference
GSTT1 & GSTM1		Age <20	Null in M	11	10	0.5 (0.2–1.7)
GSTT1 & GSTM1		Age <20	Null in T	3	1	NC
GSTT1 & GSTM1		Age <20	Both Null	5	3	0.8 (0.1–4.1)
GSTT1 & GSTM1		Age 20–24	No Null	10	21	Reference
GSTT1 & GSTM1		Age 20–24	Null in M	13	9	**3.0 (1.0–9.4)**
GSTT1 & GSTM1		Age 20–24	Null in T	2	8	NC
GSTT1 & GSTM1		Age 20–24	Both Null	1	4	NC
GSTT1 & GSTM1		Age 25+	No Null	8	45	Reference
GSTT1 & GSTM1		Age 25+	Null in M	7	27	1.5 (0.5–4.5)
GSTT1 & GSTM1		Age 25+	Null in T	1	7	NC
GSTT1 & GSTM1		Age 25+	Both Null	0	2	NC
			Vitamin use			
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)
MTHFR	rs1801133	No vitamin use	Variant	4	5	1.1 (0.2–5.1)
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	**5.1 (1.5–17.6)**
NOS3	rs10277237	No vitamin use	Wildtype	7	12	Reference
NOS3	rs10277237	No vitamin use	Hetero	9	15	1.0 (0.3–3.6)
NOS3	rs10277237	No vitamin use	Variant	7	5	2.4 (0.5–10.5)
AGT	rs699	Vitamin use	Wildtype	10	31	Reference
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*)

TABLE III. (*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	NC
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	NC
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	NC
ADD1	rs10026792	No vitamin use	Wildtype	12	25	Reference
ADD1	rs10026792	No vitamin use	Hetero	13	8	**3.4 (1.1–10.4)****
ADD1	rs10026792	No vitamin use	Variant	1	2	NC
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	2.2 (0.5–10.8)
ADD1	rs12503220	No vitamin use	Wildtype	13	25	Reference
ADD1	rs12503220	No vitamin use	Hetero	13	10	2.5 (0.9–7.2)
ADD1	rs12503220	No vitamin use	Variant	1	2	NC
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	NC
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	**0.3 (0.1–1.0)***
ICAM1	rs281432	Vitamin use	Variant	11	14	1.1 (0.4–3.2)
ICAM1	rs281432	No vitamin use	Wildtype	10	18	Reference
ICAM1	rs281432	No vitamin use	Hetero	11	9	2.2 (0.7–7.1)
ICAM1	rs281432	No vitamin use	Variant	6	5	2.2 (0.5–8.9)
ICAM1	rs3093030	Vitamin use	Wildtype	16	30	Reference
ICAM1	rs3093030	Vitamin use	Hetero	6	13	0.9 (0.3–2.7)
ICAM1	rs3093030	Vitamin use	Variant	8	9	1.7 (0.5–5.2)
ICAM1	rs3093030	No vitamin use	Wildtype	10	23	Reference
ICAM1	rs3093030	No vitamin use	Hetero	4	5	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	NC
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	NC
ICAM5	rs281417	Vitamin use	Wildtype	9	22	Reference
ICAM5	rs281417	Vitamin use	Hetero	14	29	1.2 (0.4–3.2)
ICAM5	rs281417	Vitamin use	Variant	4	3	3.3 (0.6–17.6)
ICAM5	rs281417	No vitamin use	Wildtype	4	22	Reference
ICAM5	rs281417	No vitamin use	Hetero	11	5	**12.1 (2.7–54.3)****
ICAM5	rs281417	No vitamin use	Variant	4	2	NC
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*)

TABLE III. (*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)**
			Smoking			
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	9	Reference
NOS3	rs10277237	Smoking	Hetero	3	3	2.2 (0.3–16.4)
NOS3	rs10277237	Smoking	Variant	3	1	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

TABLE IV. Haplotype Associations With Risk of Gastroschisis in Cases and Non-Malformed Controls, California 1997–2001

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, 0.2:293.8	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, 67.7:226.3	1.0 (0.6–1.6)
NOS3	CC	0.003	0.1:153.9, 1.2:292.8	NC
NOS3	GT	0.003	0.1:153.9, 1.2:292.8	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	5.3:54.7, 18.0:86.0	0.5 (0.2–1.3)
NPPA	GA	0.854	53.0:7.0, 87.0:17.0	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	0.037	0.0:60.0, 6.0:98.0	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	0.007	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	0.147	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 (0.1–2.5)
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 (0.0–33.9)
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	14.8:23.2, 33.0:51.0	1.0 (0.4–2.2)
ICAM1	CG	0.110	1.4:36.6, 12.0:72.0	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.

ACKNOWLEDGMENTS

This work would not have been possible without the tremendous leadership and scholarship of our dear colleague, Dr. Ed Lammer, who sadly passed away during the end of this research. This research was supported by funds from the Centers for Disease Control and Prevention, Center of Excellence Award U50/CCU913241, California Tobacco-Related Disease Research Program (16RT-0086) and the NIH (R00ES021470, K99ES021470, L40ES023163). We thank the California Department of Public Health Maternal Child and Adolescent Health Division for providing data for these analyses. The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the California Department of Public Health.

REFERENCES

Ahmad S, Hewett PW, Wang P, Al-Ani B, Cudmore M, Fujisawa T, Haigh JJ, le Noble F, Wang L, Mukhopadhyay D, Ahmed A. 2006. Direct

evidence for endothelial vascular endothelial growth factor receptor-1 function in nitric oxide-mediated angiogenesis. Circ Res 99:715–722.

Aicher A, Heeschen C, Mildner-Rihm C, Urbich C, Ihling C, Technau-Ihling K, Zeiher AM, Dimmeler S. 2003. Essential role of endothelial nitric oxide synthase for mobilization of stem and progenitor cells. Nat Med 9:1370–1376.

Barrett JC, Fry B, Maller J, Daly MJ. 2005. Haploview: Analysis and visualization of LD and haplotype maps. Bioinformatics 21:263–265.

Cardonick E, Broth R, Kaufmann M, Seaton J, Henning D, Roberts N, Wapner R. 2005. Genetic predispositions for thromboembolism as a possible etiology for gastroschisis. Am J Obstet Gynecol 193:426–428.

Castilla EE, Mastroiacovo P, Orioli IM. 2008. Gastroschisis: International epidemiology and public health perspectives. Am J Med Genet C Semin Med Genet 148C:162–179.

Croen LA, Shaw GM, Jensvold NG, Harris JA. 1991. Birth defects monitoring in California: A resource for epidemiological research. Paediatr Perinat Epidemiol 5:423–427.

Feldkamp ML, Bowles NE, Botto LD. 2012. AEBP1 gene variants in infants with gastroschisis. Birth Defects Res A Clin Mol Teratol 94:738–742.

Feldkamp ML, Carey JC, Pimentel R, Krikov S, Botto LD. 2011. Is gastroschisis truly a sporadic defect?: Familial cases of gastroschisis in Utah, 1997 to 2008. Birth Defects Res A Clin Mol Teratol 91:873–878.

Feldkamp ML, Carey JC, Sadler TW. 2007. Development of gastroschisis: Review of hypotheses, a novel hypothesis, and implications for research. Am J Med Genet Part A 143A:639–652.

Guo X, Cheng S, Taylor KD, Cui J, Hughes R, Quinones MJ, Bulnes-Enriquez I, De la Rosa R, Aurea G, Yang H, Hsueh W, Rotter JI. 2005. Hypertension genes are genetic markers for insulin sensitivity and resistance. Hypertension 45:799–803.

Hayflick JS, Kilgannon P, Gallatin WM. 1998. The intercellular adhesion molecule (ICAM) family of proteins. New members and novel functions. Immunol Res 17:313–327.

Jenkins MM, Reefhuis J, Gallagher ML, Mulle JG, Hoffmann TJ, Koontz DA, Sturchio C, Rasmussen SA, Witte JS, Richter P, Honein MA, National Birth Defects Prevention S. 2014. Maternal smoking, xenobiotic metabolizing enzyme gene variants, and gastroschisis risk. Am J Med Genet Part A 164A:1454–1463.

Kohl M, Wiesel A, Schier F. 2010. Familial recurrence of gastroschisis: Literature review and data from the population-based birth registry "Mainz Model". J Pediatr Surg 45:1907–1912.

Lammer EJ, Iovannisci DM, Tom L, Schultz K, Shaw GM. 2008. Gastroschisis: A gene-environment model involving the VEGF-NOS3 pathway. Am J Med Genet C Semin Med Genet 148C:213–218.

Lee PC, Kibbe MR, Schuchert MJ, Stolz DB, Watkins SC, Griffith BP, Billiar TR, Shears LL, 2nd. 2000. Nitric oxide induces angiogenesis and upregulates alpha(v) beta(3) integrin expression on endothelial cells. Microvasc Res 60:269–280.

Murohara T, Asahara T, Silver M, Bauters C, Masuda H, Kalka C, Kearney M, Chen D, Symes JF, Fishman MC, Huang PL, Isner JM. 1998. Nitric oxide synthase modulates angiogenesis in response to tissue ischemia. J Clinic Invest 101:2567–2578.

Murohara T, Witzenbichler B, Spyridopoulos I, Asahara T, Ding B, Sullivan A, Losordo DW, Isner JM. 1999. Role of endothelial nitric oxide synthase in endothelial cell migration. Arterioscler Thromb Vasc Biol 19:1156–1161.

Parker SE, Mai CT, Canfield MA, Rickard R, Wang Y, Meyer RE, Anderson P, Mason CA, Collins JS, Kirby RS, Correa A, National Birth Defects Prevention N. 2010. Updated national birth prevalence estimates for selected birth defects in the United States, 2004-2006. Birth Defects Res A Clin Mol Teratol 88:1008–1016.

Rasmussen SA, Frias JL. 2008. Non-genetic risk factors for gastroschisis. Am J Med Genet C Semin Med Genet 148C:199–212.

Rasmussen SA, Olney RS, Holmes LB, Lin AE, Keppler-Noreuil KM, Moore CA. 2003. Guidelines for case classification for the national birth defects prevention study. Birth Defects Res A Clin Mol Teratol 67:193–201.

Reefhuis J, Gilboa SM, Anderka M, Browne ML, Feldkamp ML, Hobbs CA, Jenkins MM, Langlois PH, Newsome KB, Olshan AF, Romitti PA, Shapira SK, Shaw GM, Tinker SC, Honein MA, National Birth Defects Prevention S. 2015. The national birth defects prevention study: A review of the methods. Birth Defects Res A Clin Mol Teratol 103:656–669.

Rudic RD, Shesely EG, Maeda N, Smithies O, Segal SS, Sessa WC. 1998. Direct evidence for the importance of endothelium-derived nitric oxide in vascular remodeling. J Clin Invest 101:731–736.

Torfs CP, Christianson RE, Iovannisci DM, Shaw GM, Lammer EJ. 2006. Selected gene polymorphisms and their interaction with maternal smoking, as risk factors for gastroschisis. Birth Defects Res A Clin Mol Teratol 76:723–730.

Torfs CP, Katz EA, Bateson TF, Lam PK, Curry CJ. 1996. Maternal medications and environmental exposures as risk factors for gastroschisis. Teratology 54:84–92.

Vu LT, Nobuhara KK, Laurent C, Shaw GM. 2008. Increasing prevalence of gastroschisis: Population-based study in California. Journal Pediatr 152:807–811.

Yoon PW, Rasmussen SA, Lynberg MC, Moore CA, Anderka M, Carmichael SL, Costa P, Druschel C, Hobbs CA, Romitti PA, Langlois PH, Edmonds LD. 2001. The national birth defects prevention study. Public Health Rep 116:32–40.

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