SINGLE NUCLEOTIDE POLYMORPHISMS IN VITAMIN A, FOLATE AND CHOLINE RELATED GENES AND INTERACTION WITH MATERNAL VITAMIN INTAKE AND NEUROBLASTOMA

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ABSTRACT

Angela Liu Mazul: Single Nucleotide Polymorphisms In Vitamin A, Folate And Choline Related Genes And Interaction With Maternal Vitamin Intake And Neuroblastoma
(Under the direction of Andrew Olshan)

Previous epidemiologic studies suggest maternal vitamin supplementation during pregnancy reduces the risk of neuroblastoma. We hypothesize offspring and maternal genetic variants in vitamin A, folate and choline-related genes are associated with neuroblastoma and are modified by maternal intake of vitamin A, folate, and choline

The Neuroblastoma Epidemiology in North America (NENA) study recruited 563 affected child-parent sets through the Children's Oncology Group's (COG) Childhood Cancer Research Network. We ascertained pre-pregnancy supplementation and estimated usual maternal dietary intake with questionnaires and genotyped genetic variants related to folate, choline and vitamin A pathways from DNA extracted from saliva. A log-linear model was employed to estimate additive offspring and maternal risk ratios and stratum-specific risk ratios by COG prognostic risk-classification and age at diagnosis and for gene-environment interactions. For replication for the offspring main effects, we used a genome-wide offspring case-control study from Children's Hospital of Philadelphia (CHOP).

Overall, no offspring genotypic results met criteria for a false discovery rate (FDR) Q-value<0.2 for variants related to vitamin A, folate, and choline. We found one maternal FDR-corrected maternal inverse association for a vitamin A-related SNP and neuroblastoma overall.

We found nine SNPs in/near 4 folate-related genes that were FDR-corrected significantly associated with intermediate-risk neuroblastoma but none replicated in the CHOP replication. FDR-corrected significant maternal results were found within the high-risk neuroblastoma strata and offspring age of diagnosis < 1 year with rs6776706 and rs11103603, respectively. No significant gene-environment interaction was found for pre-pregnancy vitamin supplementation. However from diet, we found a maternal rs729147-vitamin A interaction when vitamin A was dichotomized at the Recommended Dietary Allowance. Gene-choline interactions were found for offspring SNPs located in *MTHFD1L* and *TYMS*.

Our results suggest that some genetic variants involved in vitamin A and choline may be associated with neuroblastoma. The significant maternal variants and their joint effects with maternal vitamin A intake suggest a relationship between neuroblastoma and vitamin A. We also found variants related to one-carbon metabolism are not strongly associated with neuroblastoma, but some choline-related variants may play a role. However the functional consequences of these variants are unknown and require independent replication.

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5-MeTHF	5-methyltetrahydrofolate
ADH	Alcohol dehydrogenases
AdoHcy	S-adenosoylhomocysteine
AdoMet	S-adenosylmethionine
ALK	Anaplastic lymphoma kinase
ATIC	5-aminoimidazole-4-carboxamide ribonucleotide formyltransferase/IMP cyclohydrolase
BARD1	BRCA1-associated RING domain-1
BCMO1	Beta-carotene 15,15'-monooxygenase
BHMT	Betaine homocysteine methyltransferase
C	Child
CASC15	Cancer susceptibility candidate 15
CBS	Cystathionine-β-synthase
CCRN	Childhood cancer research network
CDP-choline	Cytidine diphosphocholine
CEL	Carboxyl ester lipase
CEPH	Centre de l'Étude du Polymorphisme
CES	Carboxylesterase
CHKA	Choline kinase A
CHOP	Children Hospital of Philadelphia
CHPT1	Choline phosphotransferase
CI	Confidence interval
CNV	Copy number variant
COG	Children's oncology group

CRABPI	Cellular retinoic acid-binding protein
CRalBP	Cellular retinaldehyde–binding protein
CRBP	Cellular retinol-binding proteins
DDX4	DEAD (Asp-Glu-Ala-Asp) box polypeptide 4 isoform
DFE	Dietary folate equivalence
DHFR	Dihydrofolate reductase
DHQ	Dietary history questionnaire
dTMP	Deoxythymidine monophosphate
dUMP	Deoxyuridine monophosphate
DUSP12	Dual-specificity phosphatase 12 gene
F	Father
FDR	False discovery rate
FFQ	Food frequency questionnaire
FOLH1	Folate hydrolase 1
FPGS	Folylpolyglutamate synthase
FTHFS	10-formylthf synthethase
GART	Phosphoribosylglycinamide formyltransferase, phosphoribosylglycinamide synthetase, phosphoribosylaminoimidazole synthetase
GWA	Genome-wide Association
HACE1	Encoding HECT domain–and ankyrin
HSD17B12	Hydroxysteroid (17-beta) dehydrogenase 12
HWE	Hardy Weinberg equilibrium
ICCC	International Classification of Childhood Cancer
IL31RA	Interleukin-31 receptor A precursor
INPC	International neuroblastoma pathologic classification

INSS	International neuroblastoma staging system
LCRA	Lead clinical research associate
LD	Linkage disequilibrium
LIN28B	Lin28 homolog B repeat–containing E3 ubiquitin protein ligase 1
LRAT	Lecithin retinol acyltransferase
M	Mother
MAF	Minor allele frequency
MKI	Mitosis-karyorrhexis index
MTHFD1L	Methylenetetrahydrofolate dehydrogenase 1-
MTHFD2	Methylenetetrahydrofolate dehydrogenase 2, methenyltetrahydrofolate cyclohydrolase
MTHFR	Methylenetetrahydrofolate reductase (NAD(P)H)
MTR	5-methyltetrahydrofolate-homocysteine methyltransferase
MTRR	5-methyltetrahydrofolate-homocysteine methyltransferase reductase
NBPF17P	Neuroblastoma breakpoint family member 17, pseudogene
NENA	Neuroblastoma Epidemiology in North America
NHANES	National Health and Nutrition Examination Surveys
OR	Odds ratio
OR	Odds ratio
PCYT1A	Phosphate cytidylyltransferase 1
PEMT	Phosphatidylethanolamine N-methyltransferase
PHOX2B	Paired-like homeobox 2b
PI	Principle investigator
PLD2	Phospholipase D2
PNLIPRP2	Pancreatic lipase-related protein 2

RA	Retinoic acid
RAE	Retinol activity equivalent
RALDH	Retinaldehyde dehydrogenases
RAR	Retinoic acid receptor
RARE	Retinoic acid response elements
RBP	Retinol binding protein
RDA	Recommended dietary allowance
RDH	Retinol dehydrogenases
REHs	Retinyl ester hydrolases
RFMMB	Risk Factor Monitoring and Methods Branch
RR	Risk ratio
RXR	Retinoid X receptor
SEER	Surveillance, Epidemiology, and End Results
SHMT	Serine hydroxymethyltransferase
SLC22A3	Solute carrier family 22, member 3
SLC22A4	Solute carrier family 22
SNAP	SNP Annotation and Proxy Search
SNP	Single nucleotide polymorphism
STRA6	Stimulated by retinoic acid 6
TDT	Transmission disequilibrium test
THF	Tetrahydrofolate
TYMS	Thymidylate synthetase
UNC	University of North Carolina at Chapel Hill
US	United States

CHAPTER 1. BACKGROUND AND LITERATURE REVIEW

1.1 Dissertation Aims

Neuroblastoma is an embryonic tumor arising from a malignancy within cells of the neural crest.[1,2] While 7.2% of all childhood cancers are neuroblastomas, it disproportionately accounts for 15% of all childhood cancer-related deaths.[3,4] It is the most common cancer in infancy and is thought to occur by either environmental or genetic disruption of normal embryonic development.[5] Familial cases of neuroblastoma have been associated with specific mutations in the *PHOX2B* and *ALK* genes. Among non-familial cases, recent genome-wide association (GWA) studies have identified several common variants of interest.[6-9]

Previous epidemiologic studies have found evidence of an inverse association between maternal prenatal vitamin use and neuroblastoma,[10,11] suggesting that maternal pregnancy vitamin status may play a role in neuroblastoma development. Thus, for this study we focused on three vitamins with biologic plausibility: vitamin A, folate and choline.

Vitamin A is required for many growth and developmental processes including embryonic neuronal differentiation and development.[12,13] When cultured neuroblastoma cells are treated with retinoic acid, a metabolite of vitamin A, they exhibit decreased proliferation and improved differentiation.[14,15] Folate is essential for one-carbon metabolism and is important in cell proliferation and differentiation of neural crest cells.[16,17] Choline is also involved in one-carbon metabolism and an essential building block for membrane development.[18]

Since maternal pre-pregnancy vitamin use has been previously associated with neuroblastoma and the biologic plausibility of these vitamins,[10] we are interested in common single nucleotide polymorphism in genes involved in vitamin A, folate and choline metabolism and transport pathways as well as interactions with maternal pregnancy vitamin intake from diet and vitamin supplementation.

Neuroblastoma Epidemiology in North America (NENA) is a case-parent triad study. NENA recruited families with cases of neuroblastoma under 6 years of age from the Childhood Cancer Research Network (CCRN), a registry of childhood cancer treated in Children's Oncology Group's (COG) hospitals in North America. Buccal DNA was collected from the child and both biologic parents. If the child was deceased, then banked samples were requested from COG. A self-administered questionnaire was mailed to the biologic mother to assess vitamin intake through diet and supplements pre-pregnancy and during pregnancy. It also asked for demographic data and other lifestyle factors including tobacco and alcohol use, medication use and family history. NENA recruited a total 626 parent-child trios or dyads.

Genetic effects for the offspring genotype and the maternal genotype was evaluated using log-linear models.[19 20] Additional analyses was carried out within strata defined by offspring age of diagnosis and neuroblastoma prognostic risk-classification as defined by the COG. The log-linear models was extended to test for gene-environment interactions between both the offspring and the maternal genotype and maternal early-pregnancy vitamin status.[21]

The specific aims of this project are:

Aim 1. Evaluate the association between maternal and offspring single nucleotide polymorphisms (SNPs) in genes involved in vitamin A related pathways with the risk of neuroblastoma

Aim 1a. Evaluate effects of offspring variants and maternal variants on the risk of neuroblastoma stratified by offspring age at diagnosis and neuroblastoma Children's Oncology group (COG) risk-classification.

Aim 1b. Describe the gene-environment interactions of maternal vitamin A intake during pregnancy with the offspring genotype for SNPs in the vitamin A pathway on the risk of neuroblastoma.

Aim 1c. Describe the gene-environment interactions of maternal vitamin A intake during pregnancy with the maternal genotype for SNPs in the vitamin A pathway on the risk of neuroblastoma in the offspring.

Aim 2. Evaluate the association between maternal and offspring SNPs in genes involved in folate and choline related pathways with the risk of neuroblastoma**.**

Aim 2a. Evaluate these offspring and maternal variants on the risk of neuroblastoma markers stratified by age at diagnosis and neuroblastoma risk-classification as defined by COG guidelines.

Aim 2b. Describe the gene-environment interactions of maternal folate and choline intake during pregnancy with the offspring genotype in folate and choline related pathway on the risk of neuroblastoma.

Aim 2c. Describe the gene-environment interactions of maternal folate and choline intake

during pregnancy with the maternal genotype in folate and choline related pathway on the risk of neuroblastoma in the offspring.

1.2 Neuroblastoma Overview

1.2.1 Biologic Characteristics

Neuroblastoma is an embryonic tumor of the sympathetic nervous system arising in the neural crest with embryonic origins.[1,2] Neurulation is a complicated folding process during embryogensis that transforms the neural plate into the neural tube. As the plate folds, the neural plate borders join and become the neural crest. As the neural tube closes, the neural crest is disconnected from the ectoderm. A neural tube closes, the neural crest cells migrate.[22] As these neural crest cells migrate, they further differentiate into the sympathetic nervous system. Neuroblastoma tumors are thought to derive from stem cells in the sympathetic nervous system that did not properly differentiate.

Neuroblastoma is a heterogeneous malignancy with variable site of origin, clinical presentation and cellular composition.[1] These tumors have been categorized into four basic morphologic categories:

1. Neuroblastoma (Schwannian stroma-poor)
2. Ganglioneuroblastoma, intermixed (Schwannian stroma-rich)
3. Ganglioneuroblastoma, nodular (composite Schwannian stroma-rich/stroma-dominant and stroma-poor)
4. Ganglioneuroma (Schwannian stroma-dominant)[23]

These neuroblastic tumors consist of two main cell populations, neuroblasts and Schwann cells. Since these Schwannian cells are non-malignant, these cells are likely to have been

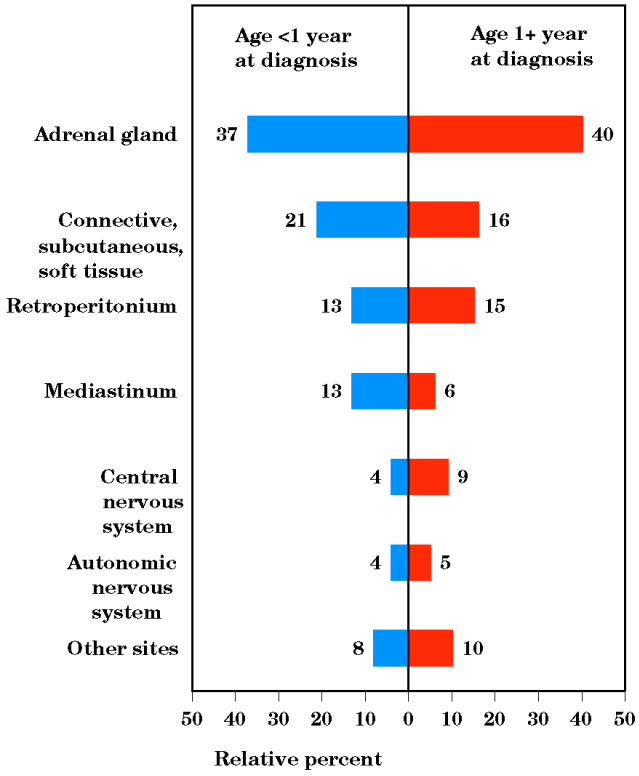
recruited by the malignant neuroblasts.[24] Schwann cells in the tumors produce anti-proliferative and differentiation-inducing factors, thus indicating less aggressive disease.[23]

Neuroblastoma tumors are less differentiated than are ganglioneuroblastoma tumors. Ganglioneuromas arise spontaneously from maturation of neuroblastic tumors (i.e. all Ganglioneuromas were once neuroblastomas in an earlier phase). Ganglioneuroblastoma falls in between neuroblastoma and ganglioneuromas in terms of differentiation.[23] In addition to spontaneous differentiation, neuroblastoma undergoes spontaneous regression more than any other cancer type, which most likely related to apoptosis of undifferentiated cells.[4] Although most clinically diagnosed neuroblastic tumors do not undergo spontaneous maturation or spontaneous regression after detection,[23] it is estimated that over 10% of cases of neuroblastoma are missed due to spontaneous regression.[25]

1.2.2 Clinical Characteristics

Neuroblastoma can arise anywhere in the sympathetic nervous system, but about 65% arises in the abdomen and over half of these in the adrenal glands. Location of the primary tumor varies by age. Children younger than 1 year of age tend to have more primary tumors in the mediastinum (the central compartment in the thoracic cavity) and children older than 1 year tend have their primary site in the central and autonomic nervous system.[26] (Figure 1)

Figure 1. Distribution of the Location of Primary Tumor by Age of Diagnosis



Reproduced from "Sympathetic Nervous System Tumors: SEER Pediatric Monograph" by M. Goodman et al., 2008.[26]

Symptoms vary depending on the location of the tumor. Approximately 50% of patients have localized or regional disease, 35% have regional lymph node spread at the time of diagnosis and the rest have widespread disease.[3] Patients with localized disease are typically asymptomatic and are often diagnosed when testing for unassociated conditions. Some symptoms include Horner's syndrome caused by primary tumors in the neck[27] and neurological impairments caused by tumors on the spinal cord.[28] However, localized tumors tend to be encapsulated and can be surgically removed. By contrast, children with metastatic disease tend to have extreme tumor burden and are very ill at diagnosis. Higher stage tumors often infiltrate to local organ systems and surround critical nerves and blood vessels, making them harder to remove.[4]

The current staging for neuroblastoma was defined by the International Neuroblastoma Staging System (INSS) and criteria are based on clinical features.[29]

- Stage 1 tumors are localized, do not involve vital structures, are confined to one body compartment and lymph nodes do not contain tumor cells.
- Stage 2A tumors are also localized and confined to one side of the body, but cannot be completely removed. Lymph nodes do not contain tumor cells.
- Stage 2B tumors are localized, but nearby lymph nodes show tumor cells. Lymph nodes on the other side of the body can be enlarged but do not contain cancer cells.
- Stage 3 tumors can fall into two categories. Either the tumor crosses the midline of the body and cannot be surgically removed, or the tumor is restricted to one side of the body, but there are enlarged lymph nodes on the opposite side of the body that contain cancer cells.
- Stage 4 tumors have spread further than stage 3 to distant lymph nodes, bone, bone marrow, liver, skin, and/or other organs.
- Stage 4S tumors tend to regress without any treatment. The criteria for these tumors are: the child is younger than 1 year of age and a localized primary tumor has only spread to the skin, lymph nodes or liver, although very small amounts may be seen in the bone marrow.

In addition to clinical characteristics, age is a very strong predictor of neuroblastoma prognosis. Children who are older than 12 months at diagnosis have lower survival rates than children who are younger than 12 months, regardless of the stage of the disease.[30] According to SEER data from 1985 to 1994, the 5-year survival for infants less than 1 year of age at diagnosis is 83%, while 5-year survival in those diagnosed from 1 to 4 years is 55%.[26]

1.2.3 Molecular Characteristics

There are many genetic aberrations commonly found in neuroblastoma tumors that are highly correlated with survival and prognosis. The genetic aberration most commonly associated with poor neuroblastoma outcomes is the amplification of the proto-oncogene *MYCN*. [31] *MYCN* amplification of 50 to 100-fold occurs in about 20% of primary tumors and is strongly correlated with advanced disease.[32,33] Somatic DNA sequence mutations have not been found in *MYCN*, suggesting that the wild-type protein is contributing to tumorigenesis or to pathogenicity of the tumor.[34] Additionally, transgenic mice that are genetically engineered to overexpress *MYCN* in the neural crest develop neuroblastoma several months after birth, suggesting MYCN can initiate tumorigenesis.[35]

The number of copies of chromosomes in a tumor cell, or ploidy, can be an important prognostic factor in children under the age of 2.[36,37] Patients with lower grade of disease tend to be hyperdiploid or near-triploid (three sets of chromosomes), while patients with a higher grade of disease are nearly diploid. [38] This is likely because whole chromosome gains and losses are associated with a defect in mitosis, leading to tumor cell death and more favorable outcomes, while more malignant tumors have a defect in chromosomal stability, resulting in chromosomal rearrangements.

Allelic loss in tumors is commonly seen in many locations and is also predictive of outcome. Allelic loss of the chromosome 11q is present in 35–45% of neuroblastoma tumors and is rarely seen in *MYCN* amplified tumors.[39,40] These aberrations are highly associated with many high risk features and prognosis independent of *MYCN* status.[41]

Recently with DNA sequencing, additional somatic changes have been identified. In one study, somatic mutations were identified in *ARID1A* and *ARID1B* in 11% of the samples and were associated with early treatment failure and decreased survival.[42] In a sample of 240 "high-risk" cases, *ALK*, *PTPN11*, *ATRX*, *MYCN* and *NRAS* were found to be somatically altered.[7] These studies revealed that high-risk neuroblastoma has markedly fewer somatic mutations than adult solid tumors, which has a stronger environmental contribution than childhood tumors. This suggests germline variants, copy number variants and epigenetic modifications drive high-risk neuroblastoma.[7,42]

1.2.4 Neuroblastoma Risk-Classifications

The Children's Oncology Group (COG) separated neuroblastoma into three prognostic risk-classifications defined by International Neuroblastoma Staging System (INSS), age at diagnosis, *MYCN* oncogene status, International Neuroblastoma Pathologic Classification (INPC), and DNA ploidy index.[43] The INPC risk-classification is based on tumor classifications, grade of neuroblastic differentiation and mitosis-karyorrhexis index (MKI) (Table 1). There are three COG prognostic risk-classifications: low-risk, intermediate-risk and high-risk (Table 2). Although these categories are prognostic, there is little evidence that favorable tumors progress to unfavorable tumors, suggesting they may be etiologically distinct.[44] Brodeur et al. demonstrated that 60 patients without *MCYN* amplification did not change *MCYN* status.[45] However the relationship of these prognostic risk-classifications with tumorigenesis remains unclear.

Table 1. International Neuroblastoma Pathologic Classification

Morphologic categories	Age	Pathology Classification	Prognostic Category
Neuroblastoma	< 1.5 yrs	Poorly differentiated or differentiating & low or intermediate MKI tumor	Favorable
	1.5–5 yrs	Differentiating & low MKI tumor	
	< 1.5 yrs	Undifferentiated tumor or high MKI tumor	Unfavorable
	1.5–5 yrs	Undifferentiated or poorly differentiated tumor or intermediate or high MKI tumor	
	≥5 yrs	All Tumors	
Ganglioneuroblastoma, intermixed	Any	Any	Favorable
Ganglioneuroma	Any	Any	Favorable
Ganglioneuroma, nodular	Any	Any	Unfavorable

Yrs: Years; **MKI:** Mitosis-karyorrhexis index

Table 2. Children Oncology Group risk-classification

Risk	INSS Stage	Age	MYCN	INPC Classification	DNA ploidy
Low risk	1	Any	Any	Any	Any
	2A/2B	<12 mos	Any	Any	Any
		≥12 mos	Non-Amplified	Any	-
		>12 mos	Amplified	Favorable	-
	4S	< 12 mos	Non-Amplified	Favorable	>1
Intermediate Risk	3	< 12 mos	Non-Amplified	Any	Any
		≥12 mos	Non-Amplified	Favorable	-
	4	< 18 mos	Non-Amplified	Any	Any
	4S	< 12 mos	Non-Amplified	Any	=1
		< 12 mos	Non-Amplified	Unfavorable	Any
High Risk	2A/2B	≥12 mos	Amplified	Unfavorable	-
	3	< 12 mos	Amplified	Any	Any
		≥12 mos	Non-Amplified	Unfavorable	-
		≥12 mos	Amplified	Any	-
	4	<12 mos	Amplified	Any	Any
		≥18 mos	Any	Any	-
	4S	<12 mos	Amplified	Any	Any

INSS: International Neuroblastoma Staging System; **INPC**: International Neuroblastoma Pathological Classification; Mos: Months; -: Not Applicable

Treatment is dependent on prognostic category of the neuroblastoma. Treatment for low-risk neuroblastoma is generally only surgery. Intermediate neuroblastoma is usually surgically removed followed with low-dosage chemotherapy. High-risk neuroblastoma has intensive

treatment of surgery, radiation and chemotherapy followed preventative medication (usually 13-cis-retinoic acid) for a year.

1.3 Neuroblastoma Descriptive Epidemiology

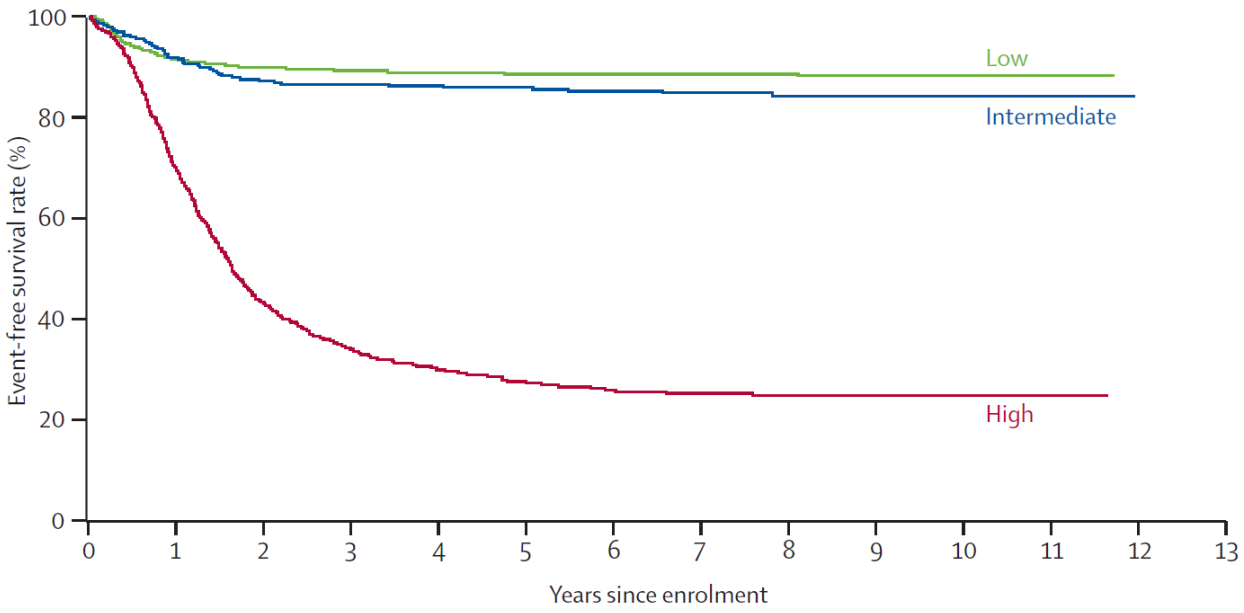
1.3.1 Incidence and Mortality in the United States

Each year approximately 1,500 cases in Europe, 700 cases in the United States (U.S.), and 70 cases in Canada are diagnosed with neuroblastoma.[2,46,47] The overall age-standardized incidence rate according to Surveillance, Epidemiology, and End Results (SEER) from 2006 to 2010 is 7.83 per million. However, the neuroblastoma incidence rate is higher among younger children. The average annual age-standardized incidence rate of neuroblastoma is 54.1 per million person-years for children less than 1 year old, 18.8 per million person-years for children 1 to 4 years old and 3.0 per million person-years for children 5 to 9 years old. Incidence of neuroblastoma is slightly higher in males than in females (7.7 per million vs 6.9 per million).[48] The difference in incidence by gender is greatest in infants under 1 year of age.[26] There are also racial/ethnic trends in incidence. European Americans have a higher rate of infant neuroblastoma than African Americans, but this trend does not persist in older children aged 1 to 14 years old and could be due to differences in detection.[26,48]

Most neuroblastoma cases fall into the COG high-risk prognostic classification. In a COG clinical cohort, 34% of neuroblastomas were low-risk, 20% were intermediate-risk and 46% were high-risk.[49] There was a higher proportion of high-risk neuroblastoma in African Americans (54%) and Native Americans (68%) than European Americans (44%). In this cohort, Asian Americans and Hispanic populations had a lower proportion of high-risk neuroblastoma than African Americans. However, the number of cases was small and solid conclusions cannot be drawn. [49]

Although the five-year survival rate for all neuroblastoma is 69%, this is highly variable by COG risk-classification. The five-year survival for high-risk neuroblastoma is about 20%.[1,50] Both low-risk and intermediate-risk neuroblastoma have a good survival rate of about 90% to 95%.[4] Because of the difference in proportion of high-risk neuroblastoma by race, 5 year overall survival and 5 year event-free survival is highly correlated with race.[49] Figure 2 shows the survival curves stratified by risk-group over enrollment in COG from 1986 to 2001. This figure shows that high-risk neuroblastoma has very poor survival that plateaus around 5 years after enrollment in COG.

Figure 2. Neuroblastoma survival curves stratified by risk type



Produced from "Neuroblastoma" by J. Maris, M. et al., 2007, *Lancet*, 369: 2111.[4]

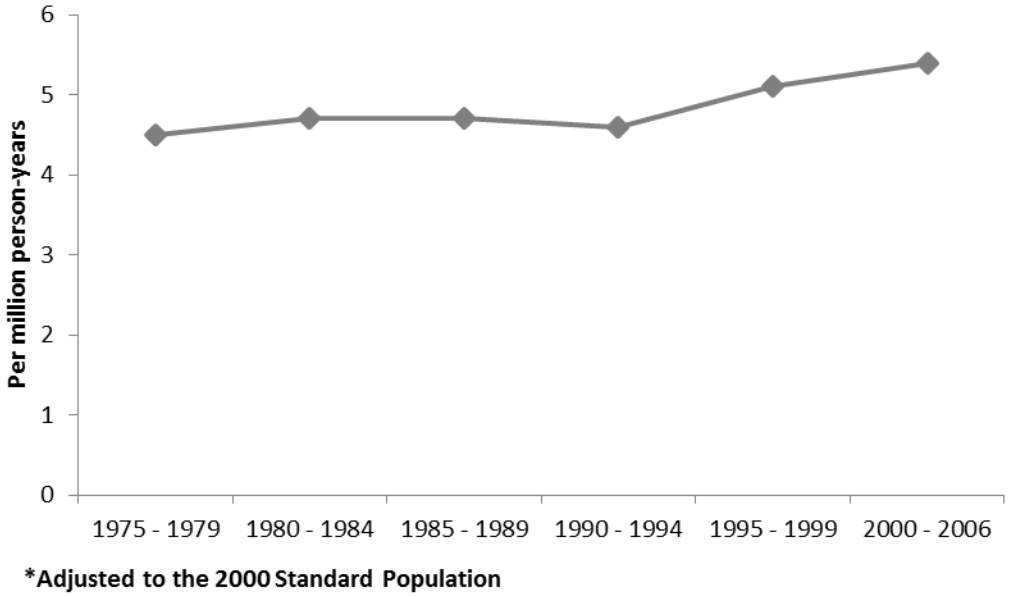
Aside from mortality, neuroblastoma also presents with life-long sequelae. About 50% to 60% of high-risk neuroblastoma cases relapse.[1] Treatment for neuroblastoma can lead to lasting effects in the survivors such as growth and developmental delays and loss of function in related

organs.[51-53] Neuroblastoma and its sequelae have been shown to cause strain on the family unit and contribute to learning and psychological distress. The 20-year incidence of chronic health conditions in survivors of neuroblastoma is 41%.[2] These lasting effects, along with the high mortality, emphasize the need to improve prevention of neuroblastoma.

1.3.2 Time Trends in the United States

The incidence of neuroblastoma in the United States has not changed in recent years. In a study from SEER, the annual percent change from 1994 to 2004 was not statistically significantly different from 0 [Annual percent change = -0.6 (95% confidence interval: -2.2, 3.5)].[48] Figure 3 displays the changes in incidence rate of neuroblastoma in SEER from 1984 to 2006 in five year increments, which also shows no change in the incidence of neuroblastoma, even after folic acid supplementation of foods in the U.S. in 1997.[54] There also have not been changes in neuroblastoma incidence by race or gender.[48] Although a study from the Greater Delaware Valley Pediatric Tumor Registry showed a rise in neuroblastoma incidence over from the 1970 to the 1989, [55] this rise is most likely due to changes in imaging technology and increased awareness.

Figure 3. Incidence rate in millions of person-years of neuroblastoma from 1975 to 2006 directly standardized to the 2000 population



Adapted from "Incidence, Survival, and Prevalence of Neuroendocrine Tumors Versus Neuroblastoma in Children and Young Adults: Nine Standard SEER Registries, 1975-2006" by Navalkele et al., 2007, *Pediatrics Blood & Cancer*, 56. [54]

Overall survival has been improving for neuroblastoma in the United States.[56] From 1975 to 2006, mortality over all ages has declined from 75% to 40%. Since infants have more favorable outcomes, survival for infants with neuroblastoma has been relatively stable since the mid-1970's with five year survival ranging from 87% to 95%. Although older children tend to have less favorable outcomes, 5-year survival rates have improved from 35% in the 1970s to 65% in 2002 possibly due to better treatment options.[57]

1.3.3 International Incidence and Time Trends

Neuroblastoma incidence varies widely around the world. Higher-income countries tend to have higher incidence of neuroblastoma than middle-income or lower-income countries.[58] In a report for the World Health Organization, Asia (with the exception of Japan and Hong Kong) and Sub-Saharan Africa have the lowest rates of neuroblastoma.[59] Countries with lower

standards of medical care and technology are less likely to incidentally diagnose neuroblastoma that does not present clinically. Similarly, survival in neuroblastoma has seen dramatic improvement from the 1980's in higher-income countries, while lower income countries have improved at a slower rate. [60,61]

Incidence rates have been increasing in Europe, but this trend is most likely due to better diagnostic tools and improving ability to differentiate neuroblastoma from other types of cancer.[62] Neuroblastoma screening has been implemented city-wide or country-wide in many countries including Japan, Germany and Canada.[63,64] As expected, these regions have experienced an increased incidence of neuroblastoma.[65] However, these programs did not lower the number of high-risk tumors or deaths related to neuroblastoma and were all abandoned.[63,64] These screening programs were most likely detecting low risk cases that would not have been previously clinically detected and regressed without treatment.

1.4 Neuroblastoma Risk Factors

1.4.1 Genetic Basis for Neuroblastoma

Neuroblastoma is both genetically and clinically heterogeneous. Cases of neuroblastoma can present with conditions associated with the sympathetic nervous system such as congenital central hypoventilation syndrome, Hirschsprung disease, pheochromocytoma, and neurofibromatosis, which suggests a shared underlying genetic cause.[9,66,67] In the 1970s, Knudson and Strong proposed that the two-stage neuroblastoma mutation model, in which two events need to occur for cancer initiation.[68] This hypothesis suggests if the first mutational event is in germline cells and the second event in somatic cells, familial cases will have an earlier age at diagnosis and be more likely to have multiple primary sites. This two-hit hypothesis has been expanded to the multiple-hit hypothesis that proposes a minimum genetic mutation threshold for

the development of disease and malignant transformation is modified by environmental exposures.[1] Common germline mutations contribute to this minimum genetic threshold, but other events must also occur for malignant transformation.

To further support this theory, the fetal environment for the tumor is very different from the infant environment. During development, humans create more cells than necessary.[69,70] As the embryo grows, the cells will go through stages of differentiation and apoptosis. In order for neuroblastoma to be clinically detected, the tumors that arise prenatally must maintain the ability for uninhibited replication in both the fetal environment and the environment after birth. To maintain this unabated replication, somatic mutations must occur early in development and again after birth.[71] In autopsies of infants whose cause of death was not cancer, the incidence of neuroblast pre-cancer is higher than the incidence of neuroblastoma.[25] These tumors that regress after birth likely did not acquire the necessary hits to lose the ability to respond to apoptotic signals after birth.

1.4.1.1 Familial Neuroblastoma

About 1% of cases present with a positive family history of neuroblastoma, which implies that neuroblastoma is highly heritable.[9] Based on the pedigree of the families, it is inherited in an autosomal dominant inheritance pattern with incomplete penetrance.[72] This incomplete penetrance could be due to the spontaneous regression of the tumor and/or to protective genetic or environmental factors. Consistent with Knudson and Strong, familial patients are often diagnosed at an earlier age and with multiple primary sites.[68] Familial neuroblastoma also has a heterogeneous presentation across affected families ranging from benign disease to widely disseminated disease within the same family,[73] suggesting that both genetic and environmental factors modify the presentation of disease.

In a small subset of patients neuroblastoma also present with other sympathetic nervous systems conditions.[9] Genes involved in these comorbid conditions have been studied in relation to neuroblastoma. A loss of function in paired-like homeobox 2b (*PHOX2B*), a gene related to congenital central hypoventilation syndrome,[74] has been observed in 6.4% of familial neuroblastoma cases and almost exclusively in cases of neuroblastoma with associated conditions of the neural crest.[75]

Given the rarity and the incomplete penetrance of familial neuroblastoma, identifying underlying genetic causes based on multi-case families has been difficult. Linkage analysis found a significant peak at 16p12–13 in seven families, but subsequent association analysis did not map a gene to this region.[76] Mossé et al. identified anaplastic lymphoma kinase (*ALK*) as a major familial neuroblastoma gene in a significant linkage peak on the short arm of chromosome 2 (2p23–p24) in 20 neuroblastoma families. Resequencing of coding exons revealed three distinct germline mutations (Table 3). Families that did not have an *ALK* mutation harbored a *PHOX2B* mutation, suggesting that either mutations in *ALK* or *PHOX2B* causes familial neuroblastoma.[77]

1.4.1.2 Spontaneous Neuroblastoma

Spontaneous, or non-familial, neuroblastoma has been associated with common as well as rare germline variants. Recent genome-wide association (GWA) studies have identified common (minor allele frequency greater than 5%) genetic single nucleotide polymorphisms (SNPs) associated with neuroblastoma mostly in Europeans and European Americans.[6] Whole genome and exome sequencing have also identified rare (minor allele frequency less than 5%) germline variants.[7]

Common polymorphisms

In a GWA study of 1,032 European American cases of neuroblastoma registered in COG and 2,043 European American disease-free control subjects from the Children's Hospital of Philadelphia Health Care Network, Maris and colleagues identified three common SNPs (rs6939340, rs4712653, and rs9295536) at 6p22 within the predicted gene cancer susceptibility candidate 15 (*CASC15*).[6,78] These three SNPs are in high linkage disequilibrium (LD; r^2 = 0.731-0.873) and yield allelic odds ratios that range from 1.39 to 1.40. These three SNPs were also significant in two replication series, one of high-risk cases in COG and another from the United Kingdom. When stratified by risk type, these SNPs were overrepresented in high-risk cases and among cases with aggressive disease. Two SNPs at chromosome 20p11 (rs3790171 and rs7272481 within *SLC24A3*) were also genome wide significant, but did not retain significance after adjustment for population substructure.[6]

A second GWA study was conducted limiting the cases to the 397 high-risk cases and the same 2,043 controls. In this subset, the previously identified SNPs remained significant and an additional six common intronic SNPs (rs3768716, rs17487792, rs7587476, rs6712055, rs6435862, and rs6715570) in *BARD1* (BRCA1-associated RING domain-1) were also significant in both the discovery and replication sets.[79] These six SNPs, located in the 2q35 locus and are in relatively high LD (r^2 =0.47–0.96). The odds ratios for these SNPs ranged from 1.59 to 1.63 in the discovery set. Genome wide significant associations were not seen between these SNPs in *BARD1* and low-risk or intermediate-risk neuroblastoma. *BARD1* has also been implicated with other cancers since it is closely related to *BRCA1* (Breast cancer 1, early onset), a tumor suppressor gene that is associated with increased risk for breast, ovarian and prostate cancer. [79] *BARD1* heterodimerizes with *BRCA1* and is thought to be necessary for the tumor

suppression function of *BRCA1*. There is no interaction observed between the most significant SNPs in the 6p22 locus and the 2q35 locus in this study.

Researchers have also identified a common germline copy number variant (CNV) associated with neuroblastoma in the same case-control study.[80] The deletion polymorphism spans less than 145 kb at 1q21.1 located within neuroblastoma breakpoint family member 17, pseudogene (*NBPF17P*). Expression of this transcript is associated with the underlying CNV genotype in neuroblastoma tumors and with expression in fetal brain and sympathetic nervous systems in normal tissue. There were no significant interactions of this CNV with previously associated 6p22 risk alleles.

Another GWA study was conducted with the original case group expanded to 1,627 and the original controls to 3,254. This study replicated the previous two loci and discovered two additional SNPs, rs4758051 and rs110419, with moderate LD (r^2=27) within *LMO1* (LIM domain only 1) at 11p15.4. The additive odds ratios combined across the discovery and all replication sets are 1.28 (95% Confidence Interval (CI):1.19, 1.37) and 1.34 (95% CI: 1.25, 0.44) for rs4758051 and rs110419, respectively. Similar to the SNPs in the 2q35 and 6p22 locus these SNPs are also significantly associated with offspring age at diagnosis older than 1 and high-risk neuroblastoma. [81] Additionally, the authors found that the *LMO1* locus is also aberrant through a duplication event in 12.4% of the tumors. *LMO1* encodes a transcriptional regulator and has been previous associated with acute lymphoblastic T-cell leukemia. [82] Germline SNPs and somatic copy number gains are associated with increased expression of *LMO1*, suggesting a role in tumorigenesis.

Nguyen and colleagues developed a gene-centric method to analyze the association of 15,885 genes annotated in UCSC Genome Browser with neuroblastoma in the expanded GWA study of 1,627 cases and 3,254 controls.[83] In addition to identifying previously significant genes, the dual-specificity phosphatase 12 gene (*DUSP12*) at chromosome band 1q23.3 was also associated. When the sample was restricted to a subset of 574 low-risk cases and 1,722 matched control subjects, *DUSP12* along with three genes in two chromosome bands (5q11.2 and 11p11.2) were significant. *DDX4* (DEAD (Asp-Glu-Ala-Asp) box polypeptide 4 isoform) and *IL31RA* (interleukin-31 receptor A precursor) are located in 5q11.2. *HSD17B12* (hydroxysteroid (17-beta) dehydrogenase 12) is located at chromosome band 11p11.2. *DUSP12* contains 1 SNP and *HSD17B12* contains 3 SNPs that were genome-wide significant, while *IL31RA* and *DDX4* did not include any SNPs that were genome-wide significant. There was no significant interaction among these three loci (p-value ranges from 0.45–0.91).

The GWA study was further expanded to 2,101 neuroblastoma cases from the COG in North America and 4,202 control subjects of European ancestry. Two additional loci, one at chromosome 4p16 with 1 SNP (rs4696715) and another at 6q16 with 2 SNPs (rs4336470 and rs9404576), were discovered. However, SNPs in high LD with the SNP at chromosome 4p16 were not associated with neuroblastoma. Upon closer examination of 6q16, 4 additional SNPs were associated with neuroblastoma (rs4079063, rs2499663, rs2499667, and rs17065417). Rs4336470 is located within the *HACE1* gene (encoding HECT domain–and ankyrin) and is in moderate LD with 3 additional SNPs (rs4079063, rs2499663, and rs2499667). Rs17065417 is located within an intron of the *LIN28B* gene (encoding lin-28 homolog B repeat–containing E3 ubiquitin protein ligase 1). Low *HACE1* expression and high *LIN2B* expression are both associated with worse overall survival.[8]

Another candidate gene analysis based on imputed genotypes was conducted with the *TP53* locus with the same 2,101 cases and 4,202 controls of European ancestry. Two imputed rare variants rs35850753 and rs78378222 (minor allele frequency= 3.0% and 1.0%, respectively) were significant at a genome-wide level. In 176 case patients, the imputed SNPs were genotyped and there was 96% concordance between the measured and imputed genotypes at those loci. Additionally, these results were replicated in an African ancestry cohort with 365 cases and 2491 controls through imputation. PCR genotyping was performed on 351 neuroblastoma case patients and 780 control subjects in an Italian cohort. The effect estimate was in the same direction and statistically significant. When pooled across the replication sets the estimated OR for rs35850753 was 2.7 (95% CI: 2.0,3.6) and for rs78378222 was 2.3 (95% CI: 1.8,2.9).[84]

Two small candidate SNP studies were conducted on Brazil. The first was a case-control study that evaluated folate-related SNPD (*MTHFR* C677T and A1298C, *MTR* A2756G, *TYMS* 2R/3R and *SLC19A1* G80A) in 31 Brazilian cases and 92 controls. *MTHFR* C677T, *MTR* A2756G and *TYMS* 2R/3R trended in a positively, but were non-significant. *SLC19A1* G80A was significantly associated with neuroblastoma (5.17; 95% CI: 1.45, 18.43).[85] Another case-mother dyad of 64 case-mother pairs and 222 control-mother pairs investigated associations with *MTHFR* C677T and *SLC19A1* G80A. Null maternal and offspring associations were seen for *MTHFR* C677T, but positive associations were seen for both maternal (G/A OR: 3.09; 95% CI: 1.02, 9.31; A/A OR: 3.16; 95% CI: 0.93, 10.67) and offspring (G/A OR: 2.48; 95% CI 1.13, 5.44); A/A OR: 3.46; 95% CI: 1.45, 8.24) associations of *SLC19A1* G80A.[86] These offspring and maternal associations are not mutually adjusted for and thus the offspring associations could be confounded by the maternal associations.

Sequencing results

Recently whole genome and exome sequencing completed on tumors and whole blood from neuroblastoma patients to investigated germline variants associated with neuroblastoma. Genes that harbored clinically annotated variants from the ClinVar database and loss-of-function variants in cancer genes were identified in the 222 cases compared to the 1,974 adult European American controls from the Exome Sequencing Project,.[7] Five candidate genes were nominated as having putative germline pathogenic variants: *ALK*, *CHEK2*, *PINK1*, *TP53*, and *BARD1*.[7] Two genes, *BARD1* and *ALK*, were previously identified in GWA studies.[77,79] *CHEK2* is has been previously linked with breast and prostate cancer.[87,88] *TP53* is associated with Li-Fraumeni syndrome, which greatly increases the risk of cancer and has been reported in neuroblastoma families.[89] *PINK1* has been previously associated with early-onset Parkinson's disease[90].

Summary.

Knudson and Strong proposed that early life cancers have a genetic basis and that familial cases present earlier and with multiple primary sites, as seen in neuroblastoma. Numerous studies suggest that there are common variants that are associated with neuroblastoma. Because of the changing fetal environment, there is evidence that neuroblastoma has an underlying genetic basis that is modified by the environment. Table 3 provides a summary of all the studies and the variants that have been associated with neuroblastoma. Although these studies did not find an association between variants within vitamin pathways and neuroblastoma, these studies are genome-wide and may not be adequately powered to find small effects in a few genes due to correction for multiple testing. In addition to genetic factors, neuroblastoma can be influenced by environmental factors, such as the fetal environment.[2] Current studies have not looked at maternal genetic effects and interactions with the maternal environment.

Table 3. A summary of genes related to neuroblastoma predisposition from Familial and GWA Studies

Gene	Variants	Neuroblastoma Subtype	Cytoband	OR (95% CI) for SNP or most significant SNP	Gene Function from NCBI gene[78]	Ref
PHOX2B	Rare Mutation	Familial	4p13	—	Promotes the development of neuronal development and differentiation in the neural crest	75
ALK	Rare Mutation	Familial	2p23.1-.2	—	Regulates the proliferation of nerve cells	77
CASC15	rs6939340	High-risk	6p22	1.37 (1.27–1.49)[a]		6
	rs4712653			1.35 (1.24–1.46)[a]		
	rs9295536			1.32 (1.22–1.43)[a]		
BARD1	rs3768716	High-Risk	2q35	1.68 (1.48–1.91)	Control cell growth and proliferation and involved with BRCA1 repairing DNA	79
	rs17487792			1.68 (1.47–1.92)		
	rs7587476			1.61 (1.41–1.84)		
	rs6712055			1.56 (1.37–1.78)		
	rs6435862			1.68 (1.49–1.90)		
	rs6715570			1.58 (1.39–1.79)		
NBPF17P	CNV		1q21.1	2.23 (1.77–2.82)	Duplicated gene associated with development	80
LMO1	rs4758051	High-Risk		1.28 (1.19–1.37)	Transcriptional regulator potentially involved in neural crest cells	81
	rs110419			1.34 (1.25–1.44)		
DDX4/IL31RA	Gene-centric	Low-Risk	5q11.2	1.49 (1.23–1.81)[b]	DDX4 alters of RNA secondary structure IL31RA is involved in IL-31 activation	83
DUSP12	Gene-centric	Low-Risk	1q23.3	2.01 (1.47–2.79)[c]	Regulates members of the mitogen-activated protein (MAP) kinase superfamily	83
HSD17B12	Gene-centric	Low-Risk	11p11.2	1.674 (1.35–2.08)[d]	Converts estrone into estradiol in ovarian tissue	83
HACE1	rs4336470		6q16	1.26 (1.18–1.35)	Involved in Golgi membrane fusion and regulation of small GTPases	8
	rs9404576			1.27 (1.18–1.36)		
	rs4079063			1.20 (1.12–1.29)		
	rs2499663			1.21 (1.13–1.29)		
	rs2499667			1.21 (1.13–1.29)		
LIN28B	rs17065417		6q16	1.38 (1.23–1.54)	Suppressor of microRNA (miRNA) biogenesis	8
TP53	rs35850753		17p13.1	2.7 (2.0–3.6)[e]	Tumor suppressor protein	84
	rs78378222					
SLC19A1	rs1051266			2.51 (1.24–5.08)[f]	Involved in the regulation of intracellular concentrations of folate	86

[a]OR for all neuroblastoma subtype [b]rs10055201 [c]rs1027702 [d]rs11037575 [e]rs35850753 [f]Dominant Offspring OR

1.4.2 Environmental Exposures

1.4.2.1 Vitamin supplementation

Studies have shown that folic acid supplementation during the preconception period lowers the risk of neural tube defects as well as several childhood cancers including neuroblastoma.[48,91-93] Neural tube defects occur when the neural tube does not close fully. Since neural tube defects occur within close proximity to the neural crest, it is possible that both can arise from related errors in signaling.[71] Although the United States food supply was fortified with folic acid at the beginning of 1998,[94] women of reproductive age from 2003 to 2006 in NHANES still are estimated to have daily folic acid intake levels lower than the recommended level of 400 μg for women of childbearing age.[95,96] From 1999-2006 NHANES, 74% of women reported taking folic acid containing multivitamin/multimineral supplements at one point in pregnancy. The percentage of women taking supplements also differs by trimester. Only 63% of mothers reported taking vitamins in the 1st trimester, 80% in the 2nd trimester and 90% in the 3rd trimester.[97] Since the neural crest migration and differentiation usually begins at around 5 weeks, this usage pattern suggests that many women may not be taking supplements during the most crucial time of fetal neuronal development. In addition to lower folic acid intake, less than 3% of the US population has folic acid consumption above the tolerable upper intake level (1000μg/day), above which there may be adverse health events as set by the Institute of Medicine.[98]

Most of the epidemiological data suggests an inverse association between neuroblastoma and maternal pregnancy vitamin intake.[10,11,99] The first study to report this association included 183 neuroblastoma cases from the New York Cancer registry from 1976 to 1987. Controls were age and race matched from the New York State live birth certificate registry (N=372). The

response rate for both cases and controls were very high (85% and 87%, respectively). Since the purpose of the study was to describe the role of prenatal medication usage in neuroblastoma, no specific question about prenatal vitamin use. The prenatal vitamin data was collected from mothers who answered an open-ended question about other medications prescribed by doctors during the pregnancy. The reported unadjusted odds ratio was 0.5 (95% CI: 0.3, 0.7) for self-reported vitamin use versus no vitamin use. Due to the open-ended question used, these results may not be an accurate reflection of vitamin use.[11] In a study where neuroblastoma cases were recruited at St. Jude in the same time period, about 90% of the mothers took prescription vitamins while 3.7% of the mothers took non-prescription vitamins,[100] suggesting that most of the women taking vitamins were by prescription.

These results were replicated in the largest case-control study (530 cases and 500 controls) to date with maternal vitamin supplementation information. Cases were enrolled from COG from 1992–1994 and 73% provided interviews. Controls were recruited with random digit dialing (72% were interviewed) and matched on date of birth with the cases. Mothers were specifically asked whether vitamin or mineral supplements were used during the pregnancy with neuroblastoma by trimester. The odds ratio for daily vitamin use during the pregnancy or 1 month before pregnancy versus no vitamin use during the pregnancy or 1 month before pregnancy was 0.6 (95% CI: 0.4, 1.0), adjusted for age at diagnosis, mother's race and education. Less than daily and daily vitamin use in the first trimester had an inverse association versus no vitamin use in the first trimester [OR = 0.6 (95% CI: 0.4, 0.9) and 0.7 (95% CI: 0.5, 1.0), respectively]. Similar results were seen in the 2nd and 3rd trimester, but only daily vitamin use was statistically significant.[10] Trimester-specific data are difficult to interpret since the women who took vitamins in the 1st trimester were very likely to continue the next trimester.[10] However,

this study clearly points to an inverse association between prenatal vitamins during pregnancy and neuroblastoma.

A small German study reported a positive association between maternal vitamin use and neuroblastoma. It was conducted from 1992 to 1994 in West Germany with cases from the German Childhood Registry (N=158). Controls were randomly sampled from the local resident registration offices and matched on community and age. This study looked at multiple childhood cancers and the authors used all controls for this analysis (2,057 controls). A questionnaire assessed whether the mother took vitamin, folate, or iron supplements during pregnancy. The results were adjusted for the matching factors and sex, age, year of birth, degree of urbanization, and socioeconomic status. Mothers who took vitamin, folate, or iron supplements were 1.5 (95% CI: 1.06, 2.13) times as likely to have a child with neuroblastoma as mothers who did not take supplements. However, the proportion of vitamin supplementation among controls in this study are much lower than in other studies in the US[10,11] and Germany in 1998.[101] Additionally, this study recruited cases from West Germany, while the other studies are North American, which could explain the different vitamin supplementation pattern.

A negative association was also suggested by surveillance data in Ontario, Canada with a 60% decrease in the incidence of neuroblastoma after food fortification with folic acid began in January 1997. The incidence of neuroblastoma decreased from 1.58 per 10,000 births to 0.88 per 10,000 births. The incidence rate ratio adjusted for age at diagnosis is 0.53 (95% CI: 0.37, 0.76).[99] However, these results failed to replicate with SEER data in United States after food fortification, which began in 1998.[48] The age-adjusted incidence rate to the 2000 US Standard Population was 30 per million person-years pre-fortification and 29.5 per million person-years post-fortification. The incidence rate ratio is 0.98 (95% CI: 0.87, 1.11). The SEER analysis

excluded cases that occurred from 1995 to 1999, while the Canadian study includes these years, allowing for potential misclassification of the exposure. Additionally, there were few cases of neuroblastoma post-fortification in the Canadian study. As with all ecologic studies the results are affected by other changing factors such as variation in patterns of personal vitamin supplementation during pregnancy.

Summary

Lowering the incidence of neural tube defects has been attributed to folic acid supplementation in food and is considered one of public health's biggest successes. Although an effect of maternal prenatal vitamins and dietary vitamin intake on neuroblastoma has not been well established, there is clear suggestive evidence for a protective association. The studies that have been done are small, but the largest suggest that there is a negative association. The inconsistent results could be due to gene-environment interactions and different environmental exposure patterns. However, case-control could be biased due to selection bias, since it would be difficult for the cases, who are usually recruited from a large registry, and the controls to arise from the same population. The controls could also fail to be representative of the sample population by either self-selection in sampling, or differential recall of the exposure variable.

1.4.2.2 Other possible risk factors

There are a few other exposures, such as maternal alcohol consumption, paternal occupational exposures, maternal use of diuretics, pain medication or codeine and low birth weight that show a positive association in multiple studies. Maternal vitamin and folic acid supplementation and history of asthma have shown a negative association in some studies. More detailed descriptions of these exposures are summarized in Table 4.

Table 4. Summary of possible risk factors of neuroblastoma

Exposure	Comments	References
Maternal Alcohol Use	Most studies report a positive association with daily or binge drinking pre-pregnancy or pre-pregnancy. Two studies reported a null association	100,102-104
Electromagnetic Field	Studies have found an association or elevated odds ratio with paternal occupations that have exposures to electromagnetic fields such as those involved with power plants. One study found a null association.	105-110
Pesticides	Studies of associations with paternal or maternal occupations that work with pesticides pesticide use have been mixed with both positive and null results. A meta-analysis also found null result as well.	103,105-107,109,111-116
Other occupational exposures	Maternal exposures to hair dye or maternal occupation of hairdresser or barber either before pregnancy or during pregnancy was associated with neuroblastoma. Maternal exposures to acetone, lead, petroleum, occupation in service retail and paternal exposures creosote, dioxin, lead, petroleum, occupation materials handling have also been associated with neuroblastoma in one study.	102,106,112,117
Use of Diuretics	Three studies have identified an imprecise, but positive association with diuretics. Another study found a positive association with diuretics and antihypertensive drugs.	100,102,118,119
Use of Pain Medications or Codeine	Three studies have found a positive association with non-prescription pain relievers and codeine during pregnancy. No association was found with drugs taken for fever during pregnancy New York State study and any type of pain medication in a German study.	11,100,118,120
Birth weight	Most studies have found a suggestive positive association with low and high birth weight. However, only a few studies have adjusted for gestational age, but there is a suggestive relationship with small for gestational age babies. Studies suggest a U-shape curve in which both low birth weight and high birth weight at associated. Additionally a meta-analysis found associations with both low birth weight and high birth weight.	103,121-132
History of Asthma or Allergies	Studies have identified an inverse association between childhood allergies and later development of neuroblastoma. In one study, family history of asthma has also been associated, but in another maternal history of asthma is not.	103,133
Parental Demographics	No clear association has been seen in maternal age. There is suggestive evidence of low or high maternal age associated with neuroblastoma. However, there are many studies showing null effects. Fewer studies have looked at paternal age, but there is one study that found an association with higher paternal age.	103,106,121,122,124-126,128-131,133,134
Tobacco Use	Most studies did not find an association with maternal tobacco use. One reported a weak positive association with maternal smoking pre-conception and during pregnancy, while a couple reported non-significant elevated odds ratios. Paternal smoking has been less studied and yielded mostly null results.	100,102-104,122,127,134-136
Maternal Recreational Drug Use	A positive association with a broadly defined recreational drug use was seen in two studies. In one study, marijuana use in the first trimester had the strongest association. Another study did not find an association, but other cancer cases served as the controls.	127,137
Sex Hormones	Two studies identified a positive association, especially in stage 1 or 2 cases. However, one study with subjects reporting exposure was very small. These results failed to replicate in 3 other studies.	11,100,102,103,138

1.5 Literature on Vitamin Pathways

Epidemiologic studies have suggested that the prenatal environment is important for the risk of neuroblastoma. Maternal vitamin intake has been consistently associated with decreased risk of neuroblastoma and likely modifies the risk of mutational "hits" occurring. There are 3 vitamins that could potentially be of importance with neuroblastoma. Vitamin A is essential to the differentiation and development of neuronal cells. Since both excess vitamin A and deficiency are associated with teratogenicity, cellular levels must be kept at equilibrium to prevent birth defects. Folate and folic acid have been associated with decreased incidence of neural tube defects. Additionally folate and choline are essential to DNA and RNA repair, synthesis and methylation. Low levels of choline and folate have been associated with DNA errors that could lead to somatic changes in the tumor.

1.5.1 Vitamin A

1.5.1.1 Biologic literature

Retinoic acid (RA) is a lipophilic molecule derived from retinoids (chemical compounds related to vitamin A). RA is required for many different biologic processes including normal growth and development and is especially important in embryonic neuronal differentiation and development.[12,13] RA concentrations must be within a very narrow range in order to avoid teratogenic effects.[13] In animal models, severe maternal vitamin A deficiency can cause embryonic death. Less severe deficiencies in fetal developmental malformations include heart defects, cleft lip or palate and malformation of forelimbs.[13,139] Vitamin A excess during development also results in major embryonic defects that overlap with those in vitamin A deficiency.[140,141] In a study of women who underwent screening for vitamin A, high levels of vitamin A intake during pregnancy have been associated with birth defects of the cranio-neural-

crest tissue.[142] Excessive vitamin A intake during pregnancy occurs from supplementation.[143] Figure 4 summarizes genes and metabolites involved in vitamin A metabolism and transport.

The body does not manufacture retinoids and so they must be acquired through the diet. Vitamin A is taken into the system either in the form animal products as retinyl esters, retinol, or RA or from fruits and vegetables as beta-carotene.[144] Dietary retinol can be directly taken up in the intestine. However retinyl ester must first be converted to retinol by retinyl ester hydrolases (REHs) such as carboxyl ester lipase (CEL), and pancreatic lipase-related protein 2 (PNLIPRP2).[145,146] Beta-carotene is broken down into retinal by Beta-carotene 15,15'-monooxygenase (BCMO1). When absorbed, all retinoids are converted to retinyl esters by lecithin retinol acyltransferase (LRAT) and is stored in the liver.[147]

When needed, retinyl esters are hydrolyzed to retinol by REHs in the liver. There is a large family of REHs and the enzyme varies based on location, but in the liver CEL and carboxylesterase (CES) are mostly responsible.[145] The retinol is bound by retinol binding protein (RBP) to be secreted into the bloodstream and made available to all cells including embryonic cells by maternal transfer across the placenta.[144] However, research shows that there must be undiscovered placental transfer methods for vitamin A that are not RBP dependent, because homozygous RBP null mutant mice are viable.[148] There is evidence that blood retinyl esters can be hydrolyzed by lipoprotein lipase (LPL) in the blood and can be transferred into cells.[149] Blood levels of Retinol-RBP are very stable, except in extreme cases of insufficient intake of vitamin A, protein, calories, or zinc.[144]

The cellular uptake of vitamin A from Retinol-RBP is mediated by the transmembrane protein Stimulated by retinoic acid 6 (STRA6).[150] Retinol is then reversibly oxidized to

retinaldehyde by several alcohol dehydrogenases (ADH) and retinol dehydrogenases (RDH). Retinaldehyde is then oxidized to RA by retinaldehyde dehydrogenases (RALDH).[151] To keep a balance of RA in a cell, RA can be degraded to 4-hydroxy-RA or 4-oxo-RA, which are believed to be non-transcriptionally active [152,153] by three cytochrome p450 enzymes.[154] Since retinoids are lipid molecules, they must be bound to proteins within cells.[155] Several binding proteins have been identified including cellular retinol-binding proteins (CRBP), cellular retinaldehyde–binding protein (CRalBP) and cellular retinoic acid-binding protein (CRABPI).[155] CRBPI has been proposed to facilitate the conversion of retinol to retinyl esters for storage and the oxidation of retinol to retinaldehyde by RDHs.[156]

RA is the biologically active form and it functions as a ligand for specific nuclear receptors, retinoic acid receptor (RAR) or retinoid X receptor (RXR), which together regulate more than 500 genes.[157] All-*trans*-RA, the most abundant form of RA, binds to RAR, while 9-*cis*-RA binds to RXR.[158] Additionally, RAR binds with RXR to form a heterodimer, suggesting RXR is most likely a scaffold protein to facilitate DNA binding.[159] *In vivo* studies have demonstrated that binding to RAR is sufficient for rescuing a lethal defect in RA synthesis, while binding to RXR is not.[160] These RAR-RXR heterodimers interact with retinoic acid response elements (RARE) in the promoter region of target genes.[161]

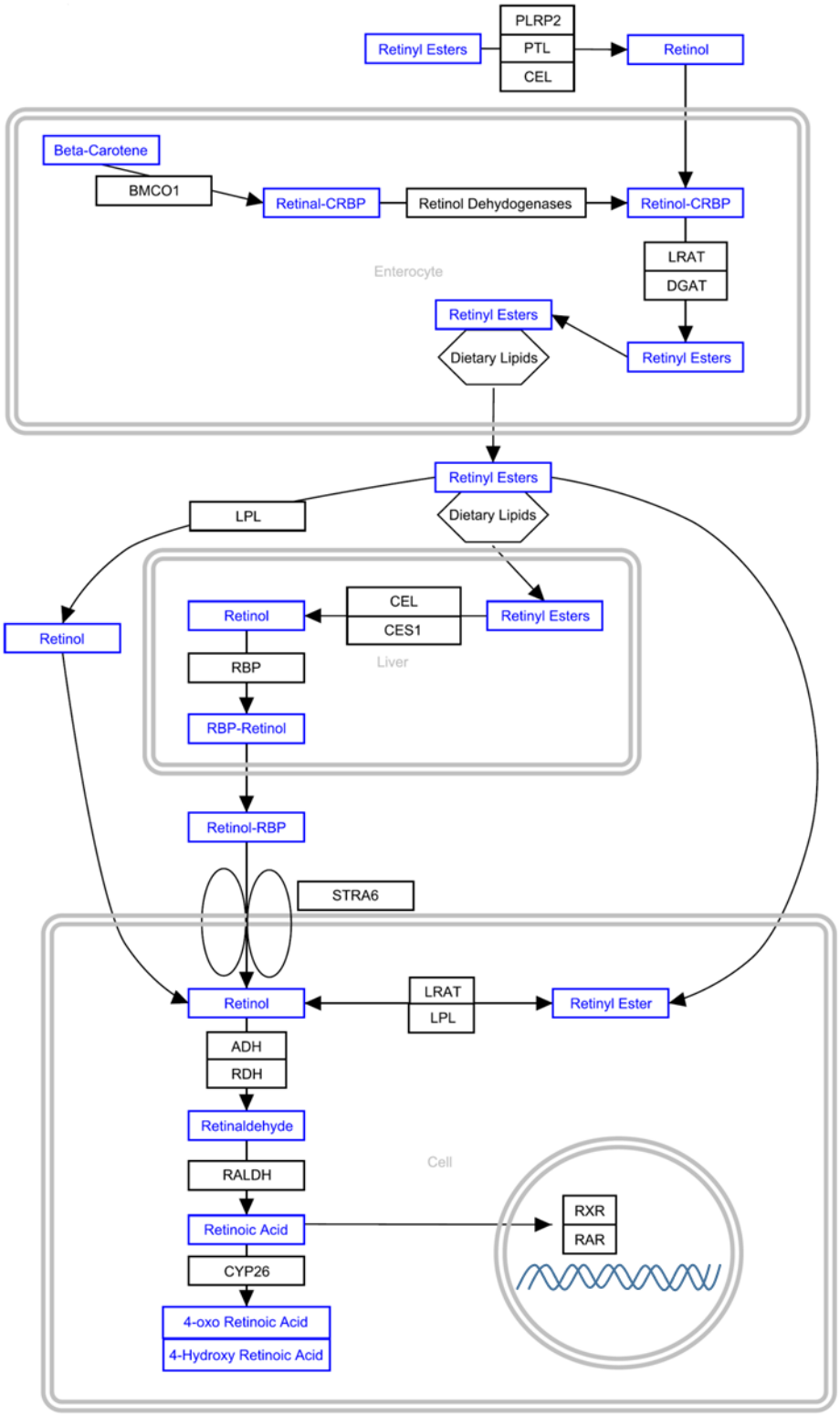
Animal models have demonstrated the importance of vitamin A metabolism and transport in fetal development. Mice that have mutations in *Rdh10* have serious defects in embryonic RA signaling resulting in embryonic death, while mice knocked out in *Adh4* and *Rdh1* do not display RA signaling alterations.[162,163] Loss of *Adh3* impairs post-natal survival, but *Adh3* has low activity for retinol oxidation, suggesting the effects may not be due to RA signaling.[164] Mice that

lack *Crbp1* have decreased stores of retinyl esters and are sensitive to vitamin A deficiency, but do not have decreased RA synthesis. [165]

Mice that are null for *Cyp26a1*, a gene encoding cytochrome P450 enzyme, have lethal morphogenetic phenotypes. These mice can be phenotypically rescued by disruption of *Aldh1a2*, suggesting that excess retinoic acid exposure induces these phenotypes.[166] Double null mutations in *Rar* in mice impair survival in utero or shortly after birth and lead to numerous vitamin A deficiency abnormalities.[167] Similar results are seen in mice with null mutations in RAR and RXR. These results showed that *Rxr-α* is the main *Rxr* involved in developmental signaling.[168]

When cultured neuroblastoma cells are treated with RA, they exhibit decreased proliferation and *MYCN* expression and differentiation.[14,15] Although survival after RA as a treatment for neuroblastoma was low,[169]13-*cis*-RA is used to prevent the recurrence of disease after treatment for high-risk neuroblastoma.[170,171] The differentiation of neuroblasts induced by retinoic acid suggests that levels of RA within the child could have an effect on the development of neuroblastoma.

Figure 4. Vitamin A transport and metabolism



1.5.1.2 Epidemiologic literature

Fetal RA level needs to be maintained at a proper concentration. Two studies have found that fetal RA has no correlation with fetal retinol levels, suggesting the variation in fetal RA levels reflects fetal generation and degradation of RA.[172,173] Common variants in *ALDH1A2* and *CRABP2* have been associated with higher cord blood retinoic acid levels in 145 healthy full-term infants.[172] A genome wide association study identified common variants near *TTR* and *RBP4* as associated with blood retinol levels in adult males.[174] Another GWA study failed to find an association with blood retinol levels, but found that rs6564851, a variant near *BMCO1*, was associated with higher blood β-carotene levels.[175] Similarly, three polymorphisms, including rs6564851 in *BMCO1* were also associated with lower catalytic activity in 28 females.[176]

Common variants within genes involved in the vitamin A pathway have been associated with neural tube defects. A case-parent triad study of 329 case-parent trios and 281 mother-child or father-child dyads found SNPs within *RARA*, *RARB*, and *RARG* to be negatively associated with meningomyelocele, a severe form of a neural tube defect.[177] Another study with 230 case-parent triads and 68 one-parent dyads found associations with 3 SNPs in *ALDH1A2* and meningomyelocele.[178] Multiple studies have found linkage in the region containing *RARA* with cleft lip/palate, suggesting these loci may harbor variants.[179-181]

Adult cancers have also been associated with variants located in the vitamin A pathway. Childhood cancer survivors are at higher risk of adult cancers. However, the reason for this increased risk is unknown since it is unclear if increased risk is due to a general genetic predisposition, to effects of the treatment, or to the original cancer.[182,183] Variants within or near the alcohol dehydrogenases have been associated with upper aerodigestive tract cancer, gastric

cancer and ovarian cancer. [184-187] Colorectal cancer, pancreatic cancer, and non-Hodgkin's lymphoma have been associated with variants in the RXR genes.[188-190] These associations could suggest that variation within these genes could be involved in malignant transformation.

1.5.2 Folate

1.5.2.1 Biologic literature

Folate is an essential B vitamin naturally found in foods and is available as folic acid in supplements and food fortification. Food folate has a reduced pteridine ring and a polyglutamate polypeptide that must be hydrolyzed in the intestinal lumen to a monoglutamate form before being absorbed by the intestinal cell and metabolized. Folic acid, which is synthetically produced to fortify foods, contains only a single glutamate and once converted to tetrahydrofolate (THF) by dihydrofolate reductase (DHFR) is identical to those from food folates.[191] Bioavailability of food folate depends on many factors such as the type of food, cooking methods of the food and genetics of the host. Studies have shown that food folate has 30% to 98% of the bioavailability of folic acid.[192,193]

Folate is necessary in one-carbon metabolism, which is involved in DNA and RNA methylation and DNA synthesis and maintenance.[194] Deficiencies in folate while pregnant have been associated with birth defects such as neural tube defects,[93,195] low birth weight,[196,197] and preterm birth.[196] Due to its association with neural tube defects, mandatory folic acid fortification of cereal products has been in place in the United States since 1997 and in Canada since 1998.[93,198]

5-methyltetrahydrofolate (5-MeTHF) monoglutamate is the main form of folate circulated throughout the body.[199] These folates are taken into the cell by folate receptors or reduced folate carriers.[200] Once in the cell, folylpolyglutamate synthase (FPGS) links multiple

glutamate residuals. These polyglutamated folates cannot be transported out of the cell, so they accumulate in the cell to keep proper cellular folate levels.[201]

One-carbon metabolism is involved in the biosynthesis of many important macromolecules such as proteins, lipids, and nucleic acids involved in cells proliferation.[16] One-carbon metabolism refers to the metabolic system that uses THF to donate or accept carbon units for cellular biosynthetic reactions and occurs in the cytoplasm, mitochondria and nucleus.[202] Figure 5 describes the one-carbon pathway in greater detail.

Briefly, during one-carbon metabolism, three major reactions occur in the cytoplasm. [202]

1. 10-formyltetrahydrofolate is the one-carbon unit involved in the synthesis of the purine ring by phosphoribosylglycinamide formyltransferase (GART) and 5-aminoimidazole-4-carboxamide ribonucleotide formyltransferase/IMP cyclohydrolase (ATIC).
2. Thymidylate synthetase (TYMS) uses 5,10-methylene tetrahydrofolate as the one-carbon unit for the conversion of deoxyuridine monophosphate (dUMP) to deoxythymidine monophosphate (dTMP).
3. 5-methyltetrahydrofolate is used in for the remethylation of homocysteine to methionine by 5-methyltetrahydrofolate-homocysteine methyltransferase (MTR) and 5-methyltetrahydrofolate-homocysteine methyltransferase reductase (MTRR).

Methionine can be converted to S-adenosylmethionine (AdoMet) by methionine adenosyltransferase, encoded by and *MAT1A* and *MAT2B*, which serves as a cofactor for methylation reactions. The primary role of mitochondrial one-carbon metabolism is to generate serine and formate for one-carbon metabolism in the cytoplasm or formylate MET-tRNA for mitochondrial protein synthesis.[16,203] Small amounts of thymidylate synthesis occur in the

nucleus. About 10% cellular folate is present in the nucleus and both TYMS and serine hydroxymethyltransferase (SHMT) have been localized in the nucleus.[204]

The regulation of cellular folate concentration is complex since it is influenced by uptake, polyglutamylation, export, and catabolism. The folate receptor Folbp1 shows localized patterns of expression in the embryo and is highly expressed in the yolk sac, suggesting this receptor is important for maternal-to-fetal transport of folate.[205] Additionally, mice that are null for *Folbp1* present with the same birth defects as mice with folate deficiencies.[206,207] During pregnancy, the need for folate increases due to the growth of the fetus, the placenta, and maternal tissues as well as a requirement for more red blood cells due to uterine enlargement and expansion of blood volume. Although there is an increased need for folate in the mother, newborns have higher red blood cell folate levels compared to maternal levels, [208,209] suggesting the importance of folate to fetal development.

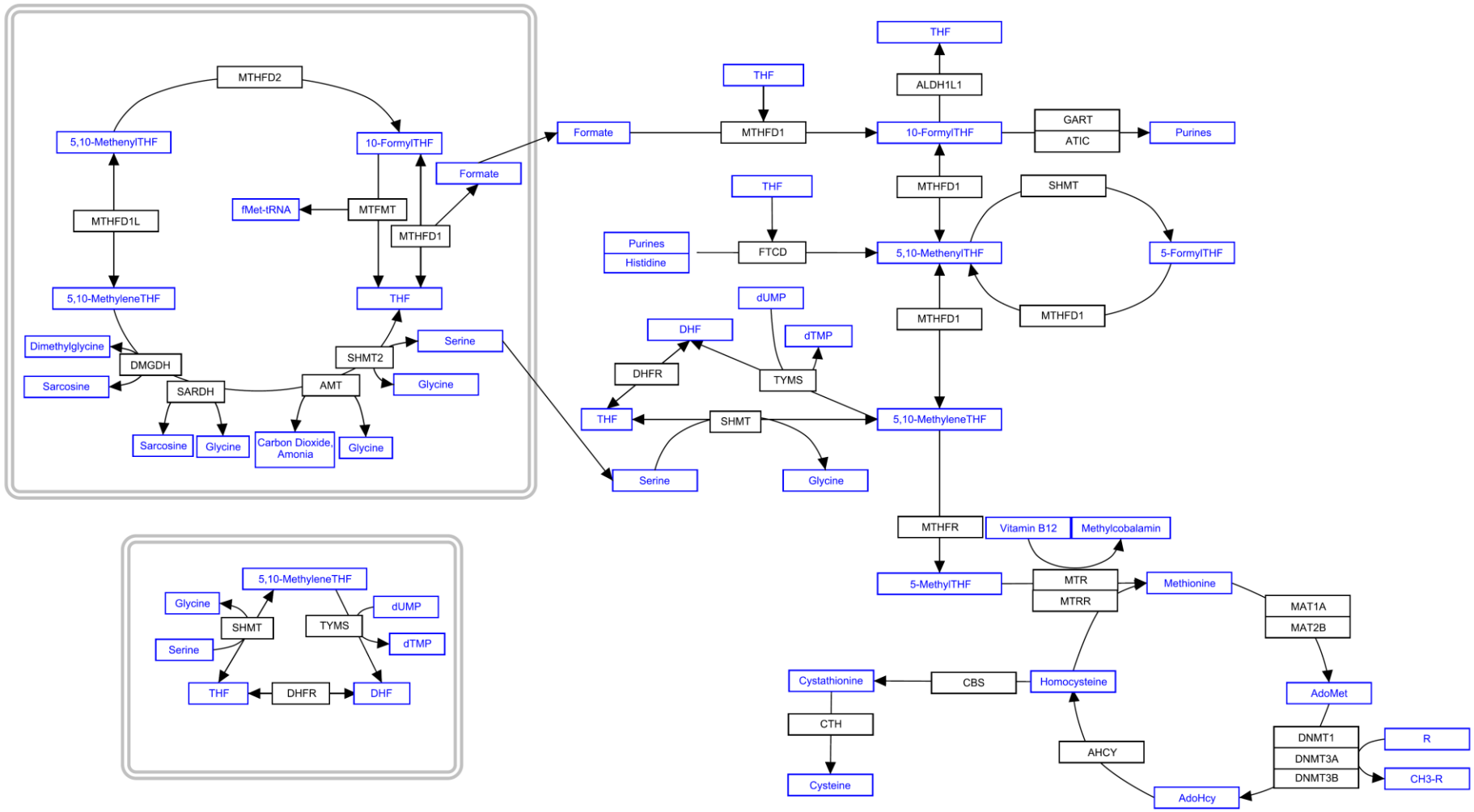
Folate transfer and polyglutamylation are critical to maintain a proper concentration of folate, and disruption of either leads to impaired folate accumulation. Folate monoglutamates can also be transferred to into mitochondria by a specific reduced folate carrier [210,211] and then converted to polyglutamated folates.[212] Because of this transfer and conversion, folate concentrations in the cytoplasm are not in equilibrium with folate concentration in the mitochondria.[191]

10-FormylTHF synthetase (FTHFS encoded by *MTHFD1*) and SHMT provide the primary entry point for one-carbon units into the network. However, one-carbon units generated by FTHFS are preferentially utilized in homocysteine remethylation and purine synthesis, while SHMT one-carbons are preferentially directed to thymidylate biosynthesis. When folate levels

are low, dUMP levels tend to accumulate, which leads to increased rates of uracil nucleotide incorporation into DNA and been associated with strand breaks and chromosomal instability.[213] Similarly, an insufficient rate of homocysteine remethylation results in an elevated plasma homocysteine, decrease in AdoMet and increase in S-adenosoylhomocysteine (AdoHcy). This leads to a decreased cellular conversion of AdoMet to AdoHcy, which is crucial for cellular methylation and results in decreased levels of 5-methylcytosine, the methylated form of cytosine, in DNA.[214,215]

Since folic acid is crucial for DNA synthesis, excess folic acid can exacerbate pre-existing cancers. Excess folic acid has also been suggestively associated with the etiology of certain cancers. In a randomized control trial in Norway, folic acid treatments in patients with ischemic heart disease was reported to increase the risk of cancer.[216] Experimental data suggest that folic acid may stimulate growth in pre-existing cancerous lesions.[217] There is likely a U-shaped curve in which both low and high levels of folic acid are important to the risk of birth defects and childhood cancer.

Figure 5. Folate metabolism and one-carbon pathway within a cell



THF: Tetrahydrofolate; **AdoMet:** S-Adenosyl methionine; **AdoHcy:** S-Adenosylhomocysteine ; **dTMP:** Thymidine monophosphate; **dUMP:** deoxyuridine monophosphate

1.5.2.2 Epidemiologic literature

Because of the association of folate with neural tube defects, variants within the one-carbon pathway have been highly studied with respect to birth defects and childhood cancer. Variants within genes involved in the one-carbon pathway have been associated with both adult and childhood cancers as well as certain birth defects.

MTHFR

The most studied gene within the one-carbon metabolism pathway is methylenetetrahydrofolate reductase (*MTHFR*), which has two common exonic variants, C677T and A1298C. MTHFR regulation is critical for AdoMet dependent reactions and regulation of homocysteine levels in the cell. The MTHFR reaction is not reversible and commits one-carbon units to methionine biosynthesis.[218] Studies have shown the low MTHFR activity may reduce DNA methylation,[215] but may enhance synthesis of thymidylate.[219]

One exonic C677T SNP (rsid: rs1801133) is one of the most common SNPs associated with *MTHFR* deficiency affecting 5 to 20% of North Americans.[220,221] This SNP has been associated with increased plasma homocysteine and decreased plasma and red blood cell folate levels, especially in those with low folate levels.[222-225] Another exonic variant A1298C (rsid: rs1801131) has also been associated with decreased enzymatic activity of *MTHFR* but to a lower extent than the C667T variant.[226] Individuals with this polymorphism exhibit increased red blood cell folate levels and homocysteine levels.

MTHFR variants has been studied in relation to birth defects and childhood cancers, including neuroblastoma. The relationship between variants in *MTHFR* and neuroblastoma was previously described. A meta-analysis found that the C677T variant is positively associated with

neural tube defects. Although there is evidence of between-study heterogeneity, all the studies have a positive trend. One study did not find an independent association with the *MTHFR* A1298C variant with neural tube defects.[227] One meta-analysis of cleft lip/palate found a positive association with maternal C677T, a suggestive association with infant C677T and null associations with A1298C.[228] Another meta-analysis found a positive association with infant C677T and cleft lip/palate in Asian populations,[229] which was replicated with a newer meta-analysis which found both a maternal and child associations with C677T.[230] Additionally, this variant has been associated with increased risk of embryonal central nervous system tumors based on a small study of Thai children.[231]

Meta-analyses have found the C677T variant to be associated with decreased risk of pediatric acute lymphoblastic leukemia, but results were null for the A1298C variant.[232,233] In addition to childhood cancers and birth defects, *MTHFR* variants have been associated with adult cancers. Although meta-analyses of adult cancers have been largely inconsistent, associations have been found with colon cancer[234-236] and ovarian cancer[237] among Caucasians, and primary brain tumors [238] among Asians with *MTHFR* C677T. One meta-analysis pooled all cancer studies together and found that *MTHFR* C677T was positively associated with cancer in the aggregate, especially in esophageal and stomach cancer and among Asians. [239]

Other Genes in one-carbon metabolism

Many other genes within the one-carbon pathway have been associated with blood folate and homocysteine levels. One exonic SNP in reduced folate carrier 1 encoded by gene *SLC19A1*, G80A (rsid: rs1051266), has been associated with decreased levels of intracellular folate through decreased efficiency of cellular uptake, but with no impact on homocysteine levels, especially in women.[240,241] Folate hydrolase 1 (*FOLH1*) C1561T (rsid: rs61886492) and

serine hydroxymethyltransferase 1 (*SHMT1*) C1420T genotype (rsid: rs1979277) have been associated with increased folate levels, but not with homocysteine levels. [222,242] [243] Decreased homocysteine levels [244-246] and increased plasma folate levels have been associated with *MTR* A2756G (Rsid: rs1805087).[247] A 19-bp deletion in *DHFR* have been associated with decreased homocysteine levels.[248] These studies show that individual folate and homocysteine levels are highly dependent on genes within the one-carbon pathway.

Since these genes can alter folate stores, they have also been associated with many birth defects. Two meta-analyses found a null, but suggestive positive association with neural tube defects and *SLC19A1* G80A, but the individual contributing studies were small and might be underpowered to detect small effects.[227,249] The meta-analysis performed by Zhang et al. did not find an association between neural tube defects and *MTR* A2756G or *MTRR* A66G. [227] Further studies have implicated SNPs within cystathionine-β-synthase (*CBS*),[250] *MTHFD1*,[251] methylenetetrahydrofolate dehydrogenase 2, methenyltetrahydrofolate cyclohydrolase (*MTHFD2*),[250] *SHMT1*, [250,252] methylenetetrahydrofolate dehydrogenase 1-like (*MTHFD1L*) [253] and *TYMS* [250] with neural tube defects.

Only a few studies investigated these variants in relation to childhood cancer. The neuroblastoma study was detailed previously. One study found that *SLC19A1* G80A was negatively associated with pediatric acute lymphoblastic leukemia in Brazilian children[254] and another found a positive association in Eastern European children.[255] Using a Bayesian approach, another study found an association between SNPs in *MTRR* and *MTHFD1* and acute lymphoblastic leukemia.[256]

The inconsistencies in results within these genes could be due to modification of genetic effects by folate levels. Some studies suggest that variants within the one-carbon pathway tend to have stronger effects among those with lower maternal folate intake. One study found that variants within *MTHFD1*, *MTHFR*, *SHMT1*, and *TYMS* were associated with neural tube defects, but only among children whose mothers had low folate levels.[252] Variants within *MTHFR* and *TYMS* have also been associated with conotruncal heart defects, but only among women in the lowest quartile of folate intake. [257,258]

In addition to the offspring genotype, the mother's genotype could also play a role in disease risk through the maternal metabolism of folate. A maternal C699T variant in *CBS* has been associated with cleft lip/palate independent of folate status.[259] One study found a positive association of unilateral retinoblastoma in the offspring and a maternal 19bp deletion in *DHFR*, even after adjustment of the offspring genotype. Interestingly, this effect is stronger among mothers who look folic acid in their first trimester.[260] Children born to mothers with variants in *MTR* pre-fortification are more likely to have acute lymphoblastic leukemia than children born post-fortification.[261]

Adult cancers have also been associated with genes within the one-carbon pathway. A meta-analysis found weak but significantly positive associations between *MTR* A2756G and *SHMT1* C1420T and prostate cancer.[262] An inverse association for a variant in *MTR* A2756G was seen with breast cancer in Caucasians, but not East Asians in two meta-analyses, while one meta-analysis found a null association.[263-265] Central nervous system cancers such as meningioma has been inversely associated with *MTRR* A66G (rsid: rs1801394) in a case control study with 631 meningioma cases, and 1,101 controls from the United Kingdom.[266] *SLC19A1*

G80A has been associated with many adults cancers including colorectal cancer,[267,268] and gastroesophageal cancer.[269]

1.5.3 Choline

1.5.3.1 Biologic literature

Choline is an essential nutrient for normal function of all cells and is critical during fetal development when it influences cell proliferation and apoptosis.[270] Although it can be synthesized de novo by phosphatidylethanolamine N-methyltransferase (*PEMT*), choline also must be consumed through the diet for normal biologic functions.[271] Choline is found in both free and esterified form in many foods. However, the foods with the highest choline levels include liver, eggs, and wheat germ.[272] Choline deficiency in adults can lead to liver and muscle damage.[273]

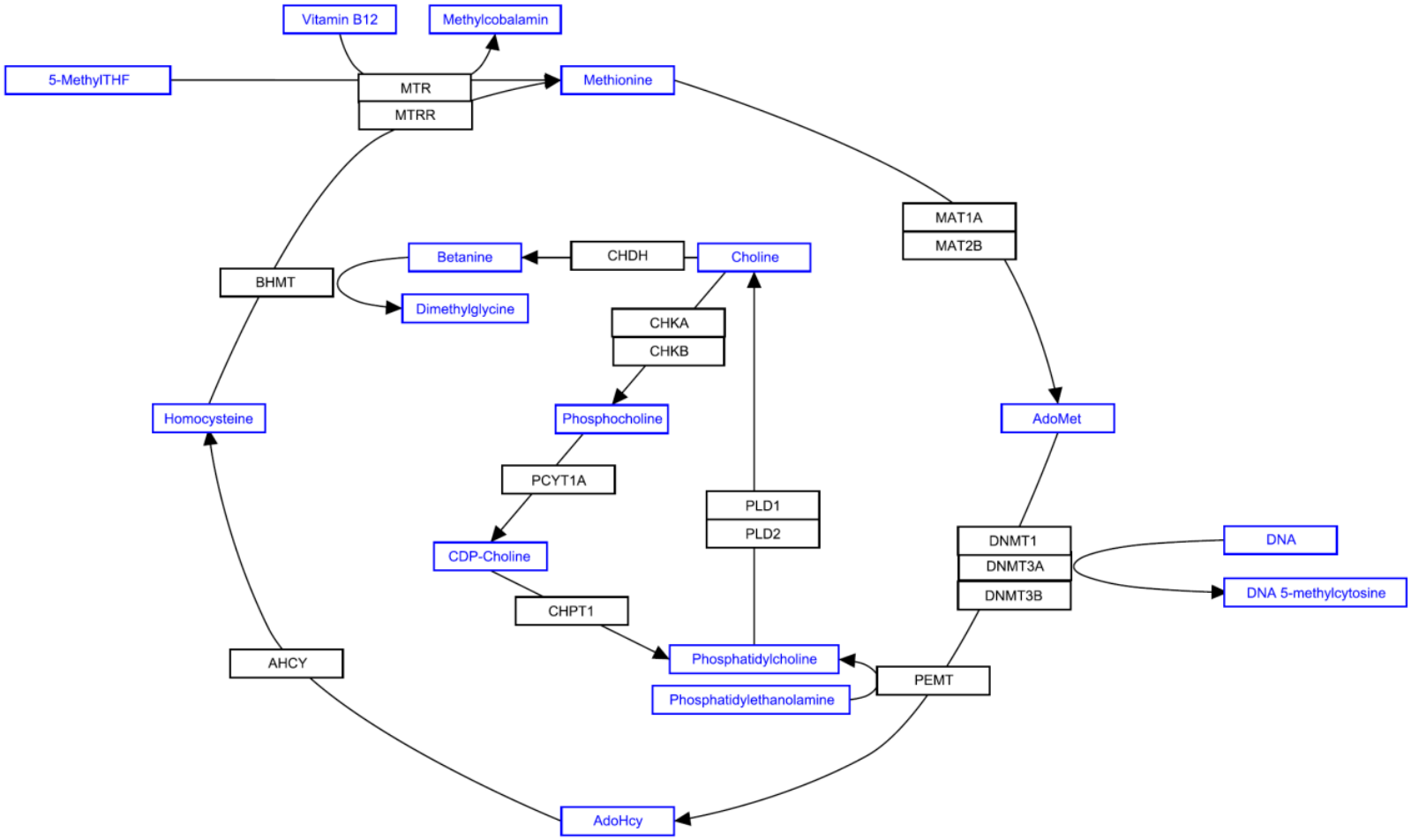
Choline is closely related to the one-carbon-pathway through a metabolite, betaine. Thus, choline is also necessary for neural tube closure. In mice, inhibition of choline leads to defects in the neural tube and face.[274] In humans, women in the lowest quartile for dietary choline, betaine, and methionine intake had almost six times the risk of having a baby with a neural tube defect compared to those in the highest quartile of intake.[275] Similar to phenotypes seen with folate deficiency, in mice choline deficiency leads to decreased stem cell proliferation and apoptosis in the brain.[276]

Pre-menopausal women tend to have fewer complications from a low choline diet than males and postmenopausal women.[277] This is due to their enhanced capacity for *de novo* choline synthesis to maintain choline stores during times of high demand for choline, such as pregnancy and lactation, [278] when cholines stores tend to be depleted.[279] Additionally, *Pemt*−/− mice abort pregnancies at around 9−10 days gestation unless fed supplemental choline.[280]

Choline is a major source of methyl groups since betaine participates in the methylation of homocysteine to methionine, as seen in Figure 6.[281] Choline dehydrogenase, encoded by *CHDH*, catalyzes the oxidization of choline into betaine aldehyde and then to betaine within the mitochondria primarily in the liver and kidney.[280] In addition to MTR, betaine homocysteine methyltransferase (BHMT) can also convert homocysteine to methionine by using betaine as methyl donor.[282] MTR is present in all tissues, while BHMT is mainly present in the liver.[283]

Choline is also used for the synthesis of the most abundant membrane phospholipid, phosphatidylcholine.[284] There are two pathways for this conversion. In one, choline is phosphorylated by choline kinase A or choline kinase B and then converted to cytidine diphosphocholine (CDP-choline) by phosphate cytidylyltransferase 1. CDP-choline is catalyzed by choline phosphotransferase (CHPT1) to form phosphatidylcholine and cytidine monophosphate. In the other pathway, phosphatidylethanolamine is sequentially methylated to form phosphatidylcholine by phosphatidylethanolamine N-methyltransferase, using AdoMet as the methyl donor.[280]

Figure 6. Choline metabolism and relationship with one-carbon pathway



AdoMet: S-Adenosyl methionine; **AdoHcy:** S-Adenosylhomocysteine

1.5.3.2 Epidemiologic literature

Dietary choline requirements for premenopausal women differ from postmenopausal women and men.[280] Premenopausal women who were carriers of *MTHFD1* G1958A (rsid: rs2236225) were 15 times as likely as non-carriers to develop signs of choline deficiency when on a low-choline diet.[285] Since *PEMT* is involved with choline synthesis, one SNP in *PEMT* G939C (rsid: rs12325817) was associated with choline deficiency in women.[286] A SNP within *CHDH*, rs12676, was positively associated with choline deficiency. *CHDH* A119C (rsid: rs9001) was inversely associated with choline deficiency[286] and homocysteine in an Indian population.[287]

Since one-carbon metabolism and choline are intertwined, SNPs within choline genes have also been associated with neural tube defects. One study found that one SNP within choline kinase A (*CHKA)*, rs7928739, was associated with decreased risk of spina bifida, while rs939883 in phosphate cytidylyltransferase 1, choline (*PCYT1A*) was positively associated. This same study did not find effect modification with maternal periconceptional choline intake.[288] Two exonic variants, rs897453 and rs7946, within *PEMT* have been shown to have a joint inverse association.[289] A variant within *BHMT* has been positively associated with neural tube defects.[250] Another study found that *BHMT* was significantly associated with neural tube defects when mothers were receiving pre-conception folic acid supplementation.[290]

Gene-gene interactions with folate-related genes were found between *MTHFR* (rs1801133), *MTR* (rs1805087), and PEMT (rs4646406) and non-syndromic isolated cleft lip with or without cleft palate.[291] Maternal gene-gene interactions have been found with *BHMT2* (rs673752), *PEMT* (rs12325817), and *PCYT1A* (rs712012) with non-syndromic isolated cleft lip with or without cleft palate susceptibility.[292]

Adult cancers have been associated with variants within these pathways as well. *PEMT* G774GC (rsid: rs12325817) and *CHDH* G432T (rsid: rs12676) were found to be associated with increased breast cancer risk in the Long Island Breast Cancer Study Project. The same study found a significant interaction between dietary betaine intake and the *PEMT* rs7926 polymorphism, where women with the variant allele with low betaine intake have 2 times the risk of breast cancer as women with high betaine intake and wildtype alleles.[293] Colorectal cancer in individuals with ulcerative colitis has been associated with variants within solute carrier family 22 (*SLC22A4*), a choline membrane protein. [294] Colorectal cancer has been associated with variants in SLC22A3 (solute carrier family 22, member 3) and phospholipase D2 (*PLD2*) in Korean and Japanese populations respectively. [295,296] A case-control GWA study identified rs9364554 in *SLC22A3* to be positively associated with prostate cancer.[297]

1.5.4 Summary of Literature on Vitamin A, Folate and Choline Pathways

Although an association between maternal intake of specific vitamins and neuroblastoma has never been studied, low levels of vitamin A, choline and folate have been associated with adverse birth outcomes including neural tube defects and some other forms of childhood cancer. These vitamins are important to the differentiation and development of cells within a developing fetus. Disruption of transport and metabolism of these vitamins can lead to poor birth outcomes similar to those with vitamin deficiency. Common variants in genes within these vitamin pathways have also been a consistently associated with both adult and childhood cancers and birth defects, including those that arise from the neural crest. Additionally variants within genes have been shown to affect uptake and levels of these vitamins and their metabolites within the body. With evidence from diseases that are similar to neuroblastoma, it is plausible that these vitamins affect the risk of neuroblastoma.

1.6 Summary of Literature Review

Neuroblastoma accounts for 28% of malignancy in infants under one year of age.[4] Each year approximately 1,500 cases in Europe and 700 cases in the United States (U.S.) are diagnosed.[2,46] Neuroblastoma has not shown the dramatic improvement in survival that has been seen with some other childhood cancers.[50] The five-year survival rate for all neuroblastoma is 69%, but the five-year survival for high-risk neuroblastoma is 20%.[1,50] Treatment for neuroblastoma can lead to lasting effects in the survivors, such as growth and developmental delays and loss of function in organs affected by the cancer.[51-53] The 20-year incidence of chronic health conditions in survivors of neuroblastoma is 41%.[2]

Currently there are no clear risk factors for neuroblastoma. Conflicting results have been reported for risk factors such as maternal or paternal smoking,[103,104,135,221] maternal medication use,[11,120] or maternal or paternal age.[122,125,131] Maternal vitamin intake [10,11] shows a suggestive inverse association. Genetic variants within vitamin-related genes could be associated with risk and interact with vitamin exposures to modify risk, as seen in other embryonic diseases. Additionally, low levels of vitamin A, folate and choline have been associated with cancer and birth defects, including some that originate from the same embryonic cells as neuroblastoma.

There is evidence for a genetic basis for neuroblastoma. Highly penetrant variants within the anaplastic lymphoma receptor tyrosine kinase (*ALK*) gene have been determined to be causal for family-based neuroblastoma, which occurs in about 1% of cases. [77] Additionally, genome-wide association (GWA) studies and sequencing studies have identified common and rare variants associated with neuroblastoma.[6,79,81]

Current GWA studies derive from the Children's Oncology Group (COG), a national clinical trials group that enrolls children with cancer from U.S. hospitals, but the controls were

recruited from the children's hospital located in Philadelphia.[6,79,81] Since neuroblastoma is rare disease, the cases are very geographically dispersed. This lack of geographically dispersed controls could introduce bias into the study due to geographic differences in allele frequencies. However, since these studies were restricted to European Americans, population stratification was likely not a factor.[298] Since there are many loci that are being tested with no a priori hypothesis, the p-values were Bonferroni corrected, which is conservative.[299] Although GWA studies are currently the standard within genetic epidemiologic studies, with rare diseases there is a need to conduct studies that are not dependent on controls and methodology to gain power without recruiting more people, such as the case-parent triad design.

Candidate pathways enable the researcher to focus on genes with a strong prior evidence and gain efficiency by selecting single nucleotide polymorphisms (SNPs) within haplotype groups[300] which allows for a targeted approach using densely measured genetic variation. Since neuroblastoma arises from the neural crest, primitive sympathetic neural precursor cells,[301] maternal vitamin A, choline and folate status and vitamin pathways can greatly influence neural differentiation and development. Animal studies have shown that dysregulation of these pathways can lead to birth defects, and epidemiologic studies have shown that genetic variants are associated with cancers and birth defects. These pathway-defined genes thus offer strong prior plausibility for a role in the etiology of neuroblastoma.

CHAPTER 2. AIMS AND METHODS

2.1 Study population

2.1.1 COG and CCRN

The Children's Oncology Group (COG) has about 200 member institutions in the United States and Canada that treat many cases of childhood cancers diagnosed in children less than 15 years of age. A study considering data from 1992 to 1997 estimated 71% of cancer cases younger than 15 years of age in the US or Canada were seen at a COG institution.[302]

The Childhood Cancer Research Network (CCRN) was created by COG to create a network that facilitated future research. The COG constitution requires that institutions register all cases diagnosed in the hospital with the case birth date, type and characteristics of the cancer, date of diagnosis, gender, race and residential zip code regardless if the patient is being treated on an active COG protocol. The parents are asked to consent to collection of personal identifiers and permission to be contacted for future non-therapeutic studies. If the parents do not consent to the collection of personal identifiers, the case is registered with a unique identifier and only the default information. If the parents do consent to the collection of personal identifiers, but do not to future contact for studies, they are registered in the CCRN with patient's and parent's names and address and a flag for no future contact. If the parents do consent to all levels, then the case is registered with personal identifiers and a flag for future contact.

In a pilot study, among those who have registered for CCRN, 93% gave permission to be contacted for future non-therapeutic studies. Only 1% refused collection of personal identifiers

and denied permission to be contacted for future non-therapeutic studies.[303] Although COG hospitals may not see all the cases and may disproportionately see cases based on race and location,[304] the CCRN is currently the only mechanism for assembling a large number of cases and obtaining DNA from cases that have died. The use of a case-parents design also protects from bias due to self-selection and guarantees internal validity because in effect the non-transmitted parental alleles are serving as controls that are ideally well-matched to the case.

2.1.2 Neuroblastoma Epidemiology in North America (NENA)

The Neuroblastoma Epidemiology in North America (NENA) study is a case-parent triad of families with neuroblastoma. Cases were eligible if they had a primary diagnosis of neuroblastoma (including ganglioneuroblastoma, but excluding ganglioneuromas; International Classification of Childhood Cancer (ICCC): 9490, 9500) before the age of 6 years at a North America COG institution, located either in the U.S. or Canada, from December 24, 2007 to July 31, 2013 and with the biologic mother alive and willing to participate. The case offspring did not have to be alive to be eligible. All eligible parent respondents understood either English or Spanish for the written questionnaire. Children over the age of 6 years were not recruited since NENA and this proposed study are interested in the etiology of early pediatric cancer and maternal exposures during pregnancy.

2.1.3 Recruitment

There are 3 phases to recruitment in NENA: institutional phase, phase I and phase II.

2.1.3.1 Institutional phase

Potential subjects were enrolled in the CCRN and agreed to be contacted for non-therapeutic studies. The contact information for these subjects and the treating institution and staff were released to the University of North Carolina at Chapel Hill (UNC) from 2007 to 2013.

In the institutional phase, NENA created a sub-registry of all potential subjects identified in the CCRN who met NENA criteria.

As many families were still going through treatment during recruitment, the treating institution was contacted first. This allowed NENA to learn the case status and better select a timeline for recruitment. A passive-consent letter sent to the principle investigator (PI) of the hospital to inform then that a patient was eligible for NENA. The PI only needed to respond if they advised a delay or avoidance of recruitment.

The institution's Lead Clinical Research Associate (LCRA) was contacted and NENA requested feedback pertaining to the family's readiness for recruitment. The LCRA Cover Letter explained the study and asked the LCRA to complete and return the Communication Guide using an enclosed prepaid Business Reply (US) or International Business Reply envelope (Canada) or to contact study staff by fax, email, or phone with their answer. The Communication Guide listed the patient's CCRN ID, and provided a space for the LCRA to note if there was any reason to delay or cancel recruitment for a particular family. Separate sections requested feedback for living and deceased cases. If no response was received within three weeks from the date of the initial mailing, a reminder letter was mailed or emailed to the LCRA, followed by an email or a phone call two weeks after that reminder mailing. The first contact was initiated at least 8 weeks after diagnosis. Procedures for contacting the parent and consent forms were different based on the offspring case status.

2.1.3.2 Case Status

These fall into three overarching recruitment categories (Alive, Deceased and Canadian). Canadian was separated out due to differences in mailing procedures due to customs. Within these categories, there are 8 types of cases that were enrolled in NENA.

Alive Cases

Unprocessed cases are families that contacted NENA prior to case recruitment. When this occurred, the staff checked their names and information about the diagnosing hospital against the registry. If the case was eligible, the staff initiated the institutional phase. The case was contacted again after the institutional phase had been completed.

Biological mothers were the first point of contact, since it was critical for NENA to assess maternal exposures. During recruitment, the mother was asked to confirm her biological relationship to the case child. If a biological mother could not be identified for a case due to surrogacy, adoption or step-parenthood, the family became ineligible for the study. If the biological mother was identified and willing to participate, the biological father, or secondary father, was then recruited separately.

Secondary fathers were recruited if the confirmed biological mother agreed that he would participate or if the study contacted the father separately.

Primary fathers were contacted if the father but not the mother was listed in the CCRN. The staff verbally confirmed his biological relationship with the child. If the father allowed verbal or written identification of and contact with the biological mother, the study could then approach the biological mother of the case child.

Guardian only cases are situations in which neither mother or father is listed in the CCRN. In these, NENA contacted the guardian and asked for contact information for the biological mother. If the mother could not be identified, the family was deemed ineligible.

Deceased Cases

There are 3 types of deceased cases, each with a different recruitment protocol: *known deceased*, *learned deceased*, and *recruited deceased*. Known deceased cases are those for whom the staff learned at the institutional stage that the case was deceased. Learned deceased cases are those for whom communication was initiated but there had been no response when the staff learned the case was deceased. Recruited deceased are cases from families that had already agreed to participate and study materials had already been mailed out when NENA staff learned the case was deceased.

Canadian cases

Canadian cases are separated out because there were customs requirements and postage/mailing needs and the families had to be made aware that incentive payments would come in the form of a check from a US bank. Other than these, Canadian cases were recruited with the same guidelines as above.

2.1.3.3 Phase I

Once an optimal time for contact was determined, a Study Introduction Letter was sent informing the parents that the child's treatment center participates for research purposes with COG and the CCRN and that more information will be coming in the mail. Most families were recruited 2 to 6 months after diagnosis.

A recruitment packet was sent 10 days after the Study Introduction Letter with more comprehensive information about study procedures and including a response form to accept or decline the invitation to be in the study. If at least one parent was willing to participate, consent forms, saliva collection kits, questionnaires and return kits were sent. If parents lived apart, the introductory letter and recruitment packet was first sent to the custodial parent. When study materials were received, families were compensated $20 for participation in this study.

A slightly different packet was sent to Canadian cases. Canadian families received an additional document called the Canadian Recruitment Insert, which summarized three details which pertained only to Canadian-based participants: 1) the prepaid Business Reply envelope was a different color than the one described in the Interest/Deceased Interest letter; 2) return mailings in Canada for the questionnaire and saliva kits had to come from a post office due to customs regulations for those size packages; and 3) compensation for returned study materials from Canadian participants would be coming in the form of a check from a US bank account.

If there was no response within a 21-day period, the NENA staff mailed a 1 page reminder about the study and invited the parent to visit the website. The flyer also stated that if the NENA staff did not hear back in 3 weeks, a staff member would call and leave a message if no one answered. NENA staff attempted up to 4 phone calls. If there was no response within 30 days of the reminder, the case was moved to Phase II and the staff did not attempt to contact the family for at least 6 months.

2.1.3.4 Phase II

If Phase I did not result in a response, before contacting families again, NENA staff conducted an in-depth search to assess optimal time to re-contact in case the child had passed

away or was still involved in treatment. If a favorable time lapse could be established, then Phase II continued similar to Phase I. Only eligible mothers who did not respond during the first phase of recruitment were eligible for a second phase of recruitment after the waiting period.

2.1.3.5 Recruitment for Deceased Cases

For recruitment for deceased cases, language was altered to be sensitive to parents of a child who recently died. Deceased Study Introduction Letter and Deceased Interest Cover Letter were used. For such families, contact was delayed to 15 months from the date of death. Deceased cases were not followed up in Phase II.

When NENA learned that that a child had died during the process of recruitment, the Learned Decease protocol replaced the current protocol. A Condolence Letter was sent expressing sympathy for their loss and respecting their need to grieve. The letter also let the parents know that the study staff would be contacting them at a later date. Although no response was required of the parent, if the parent contacted the study office with a participation decision, NENA communicated with the parent or utilized the Deceased Study Introduction Letter and Deceased Interest Cover Letter.

If the child had died during the data collection, the families were sent a Deceased Follow-Up letter, Response Form and a prepaid Business Reply or International Business Reply Envelope once 15 months had passed from the child's date of death. The letter reiterated what participation in the study involved. The parents were asked to complete a Response Form, which requested a decision about continuing their study participation. If we did not receive a response from the parent within 30 days, the letter, the form, and either a prepaid Business Reply (US) or International Business Reply Envelope (Canada) was resent. If there was no response from the

parent after the mailings, the study stopped all attempts at contact and determined that participation for that family had ended.

2.1.4 Study population

From 2007 to 2013, the diagnosing institution was contacted for 1,642 cases from the CCRN. Figure 7 is a flow chart of the data collection for NENA. Feedback from institutions was received from 1,564 of the cases and 1,379 cases had institutional approval for contact. After contact, 930 cases were determined to be eligible for the study and 870 case parents agreed to participate in the study. There were 14 "learned" deceased or "recruited" deceased children and 37 known "deceased" children. Overall, after consent, the response rate for the DNA sample was 72%, 71%, and 72% for mother, father and child respectively. The maternal questionnaire response rate was similar at 72%. Table 5 outlines the number of parent-child triads and parent-child dyads with and without DNA. There were a total of 647 case families, including 626 with a completed questionnaire and 91 dyads and 497 triads with both DNA and a completed questionnaire.

Figure 7. Flowchart of NENA recruitment

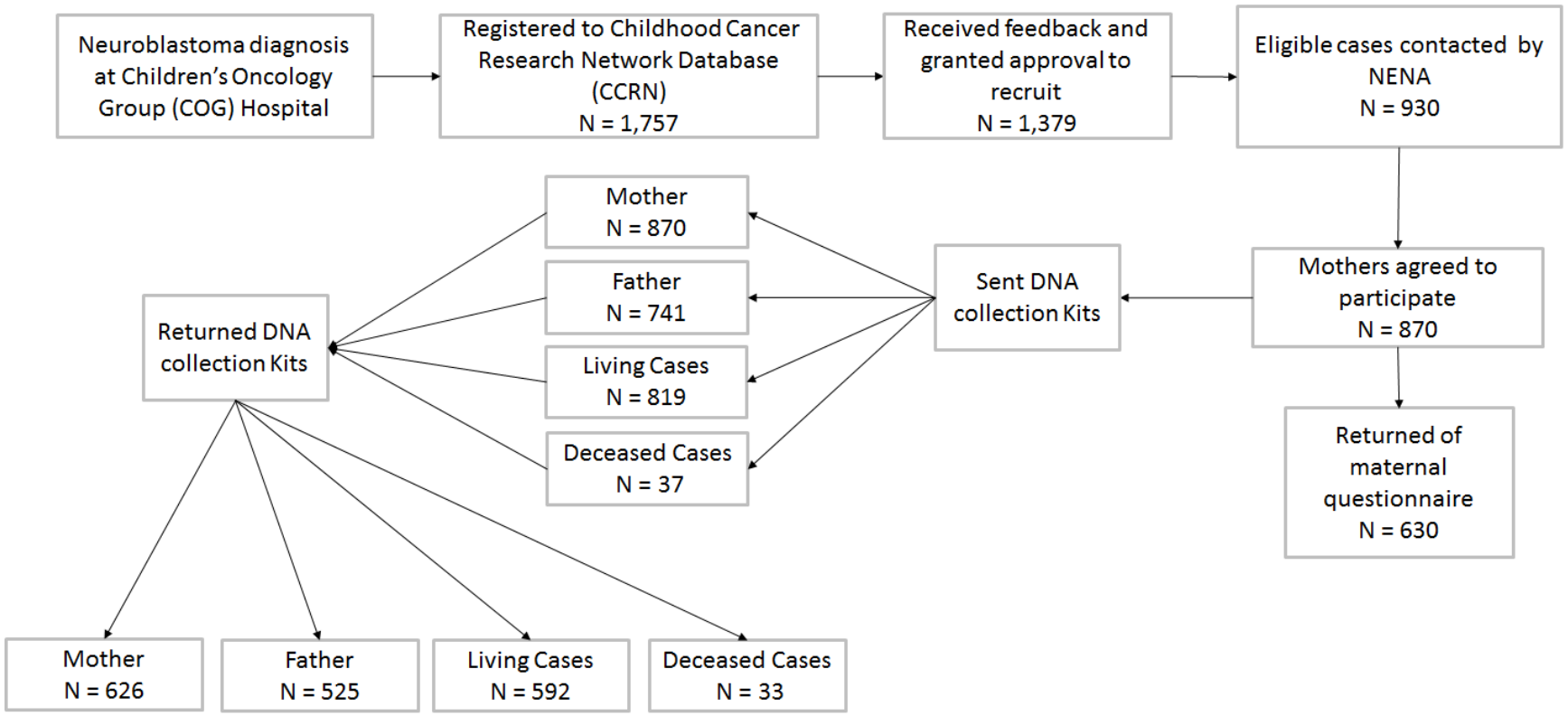


Table 5. Number of returned materials

Child Specimen	Mother Specimen	Questionnaire	Father Specimen	Number
Yes	Yes	Yes	Yes	497
Yes	Yes	Yes	No	91
Yes	Yes	No	Yes	8
Yes	Yes	No	No	6
Yes	No	No	Yes	1
No	Yes	Yes	Yes	13
No	Yes	Yes	No	8
No	Yes	No	Yes	1
No	No	Yes	Yes	1
No	No	Yes	No	16
No	No	No	Yes	3
			Total	647

2.2 Measurements

2.2.1 Clinical and Biologic outcomes

Patient clinical and biologic characteristics of the tumor were obtained from COG, including risk-classifications. (Please see 1.2.4 Neuroblastoma Risk-Classifications) for those patients who were enrolled in a COG protocol.

2.2.2 Environmental Exposures

Exposure data was assessed with a mailed paper questionnaire to be completed by the biologic mother. The questionnaire was pretested and contained modules from validated instruments and previous COG surveys. Each questionnaire also included tailored date reference sheet that included an approximate date of conception and date of each trimester as well as the offspring birth date to guide accurate recall of exposures.

2.2.2.1 Maternal Dietary Questionnaire

The main focus of the questionnaire was maternal diet during pregnancy. The current maternal usual diet was first assessed. Then information about changes in diet that may have taken place during pregnancy was elicited. Maternal usual diet was estimated through a self-

administered semi-quantified food frequency questionnaire (FFQ) called the Dietary History Questionnaire that consists of 124 food items and portion size questions developed by Risk Factor Monitoring and Methods Branch (RFMMB) of the National Cancer Institute. Replication studies demonstrated that the DHQ provides reasonably valid estimates of nutrient intake.[305] Paper questionnaires were scanned and created into an ASCII text file, which was then processed in Diet*Calc (version 1.5.0). The nutrient and food group database is based on a compilation of national 24-hour dietary recall data from the National Health and Nutrition Examination Surveys (NHANES) conducted in 2001-02, 2003-04, and 2005-06 (http://riskfactor.cancer.gov/dhq2/database/). Certain foods not included in the original database were added by NENA staff in 100 gram amounts using the USDA database, standard release 24 such as papayas and bulgur.

The original database contained information for vitamin A and folate, but not choline. Choline values common in food were included based on the USDA database. Additionally, there were foods that were not included in the original database and were included for 100 gram amounts using the USDA database.

The relevant time for assessing diet for this study would be before and during neural crest migration and differentiation which occurs about 5 weeks after conception. However, the questionnaire asked about usual maternal diet in the last year. Two previous studies examined changes in a woman's dietary patterns from preconception through postpartum. One study found no major changes in diet due to pregnancy.[306] The other study found that women tended to increase their consumption of fruits and vegetables during pregnancy and in the 2 years postpartum. However, milk consumption increased during pregnancy, but the increase did not

continue postpartum.[307] Other studies have suggested that it is important to query specifically about foods that may be subject to aversions during pregnancy such as alcohol and caffeine.[308]

To gather information about changes in diet during pregnancy, specific foods prone to change were targeted such as dairy, citrus, juices, fruit, meat, coffee, diet soda and alcohol drinks.[309] The mothers were asked if during pregnancy intake was "Much less than it is now", "Somewhat less than it is now", "Same as it is now", "Somewhat more than it is now", and "Much more than it is now". This information determined whether the mother's consumption of certain foods that are prone to change during pregnancy were different during pregnancy with the case child than her current consumption.

2.2.2.2 Maternal Prenatal Vitamin Supplementation

The questionnaire also asked about maternal vitamin and mineral supplements as well as dietary supplements during pregnancy. The mother was asked whether she took prenatal vitamins or multivitamins 1 month before conception and separately in the 1st trimester, 2nd trimester or 3rd trimester. If the mother said she did, she was then asked if she took prenatal vitamins, multivitamins or both and on average if the vitamins were taken daily, 4-6 times a week, or 3 times a week or less. Mothers were also asked if they could recall the name and the manufacturer of the vitamin, including ones prescribed by the doctor. In addition to multivitamins, single vitamins were also queried, but for the duration of the whole pregnancy.

2.2.2.3 Nutrients

From the FFQ in the NENA questionnaire, the Diet*Calc program calculated the usual nutrient intake. To assure the best quality data, the individuals below 5th percentile and above the 97th percentile of calories per day (below 854.47 and above 4508.75 calories per day) were

excluded. There were 31 mothers who reported a usual daily caloric intake less than 854.47 and 18 mothers with intake greater than 4508.75 calories per day. The nutrients of interest include total choline, total folate measured in µg dietary folate equivalence (DFE), folic acid, and vitamin A measured in µg retinol activity equivalent (RAE). DFE takes into account that folic acid has higher bioavailability than food folates. Similarly, RAE for vitamin A accounts for the differing bioactivities of retinol and provitamin A carotenoids.

Almost all of the women took either prenatal vitamins or multivitamins at some point in their pregnancy (Table 6), and by the end of the first trimester over 85% of women were taking vitamins. We decided to focus on prenatal or multivitamin supplementation pre-pregnancy, since it is the most relevant for the research question since the neural crest migrates early in pregnancy.[71] Since about 50% of the women were not able to recall the specific vitamin they took, the formulations of the vitamins could not be determined.

Table 6. Descriptive statistics of NENA. Continuous variables are represented as mean ± standard deviation and categorical variables are N (%)

		COG Risk-Group				Age Group	
	All (N = 626)	Low-Risk (N = 175)	Intermediate-Risk (N = 142)	High-Risk (N = 198)	Missing (N = 111)	< 1 year (N = 260)	≥1 year (N = 366)
Age (weeks)	87.5±74.37	75±74.49	44.5±40.07	132.8±62.29	84.5±85.36	20.5±15.14	135.6±61.91
Maternal Age (Years)	29.7±5.31	29.4±5.13	29.6±5.32	29.9±5.32	30±5.58	29.7±4.8	29.8±5.65
Vital Statistics							
Deceased	38 (6.1%)	1 (0.6%)	3 (2.1%)	32 (16.1%)	2 (1.8%)	7 (2.7%)	31 (8.5%)
Alive	585 (93.5%)	174 (99.4%)	139 (97.9%)	164 (82.4%)	108 (97.3%)	253 (97.3%)	332 (90.7%)
Unknown	3 (0.5%)	0 (0.0%)	0 (0.0%)	3 (1.5%)	1 (0.9%)	0 (0.0%)	3 (0.8%)
Gender							
Male	341 (54.5%)	87 (49.7%)	72 (50.7%)	110 (77.5%)	72 (64.9%)	147 (56.5%)	194 (53.0%)
Female	285 (45.5%)	88 (50.3%)	70 (49.3%)	88 (62.0%)	39 (35.1%)	113 (43.5%)	172 (47.0%)
Race							
White	532 (85%)	141 (80.6%)	118 (83.1%)	175 (88.4%)	98 (88.3%)	217 (83.5%)	315 (86.1%)
Black	24 (3.8%)	12 (6.9%)	3 (2.1%)	6 (3.0%)	3 (2.7%)	9 (3.5%)	15 (4.1%)
Hispanic	36 (5.8%)	13 (7.4%)	10 (7.0%)	7 (3.5%)	6 (5.4%)	20 (7.7%)	16 (4.4%)
Other	34 (5.4%)	9 (5.1%)	11 (7.7%)	10 (5.1%)	4 (3.6%)	14 (5.4%)	20 (5.5%)
Pregnancy Vitamin Use							
1 month before pregnancy							
No	247 (40.6%)	71 (41.8%)	56 (40.3%)	79 (40.9%)	41 (38.7%)	105 (41.3%)	142 (40.1%)
Yes	361 (59.4%)	99 (58.2%)	83 (59.7%)	114 (59.1%)	65 (61.3%)	149 (58.7%)	212 (59.9%)
Missing	18	5	3	5	5	6	12
1st trimester							
No	54 (8.7%)	11 (6.3%)	12 (8.5%)	22 (11.2%)	9 (8.2%)	22 (8.5%)	32 (8.8%)
Yes	569 (91.3%)	163 (93.7%)	130 (91.5%)	175 (88.8%)	101 (91.8%)	237 (91.5%)	332 (91.2%)
Missing	3	1	0	1	1	1	2
2nd trimester							
No	85 (13.7%)	19 (10.9%)	17 (12.0%)	37 (19.0%)	12 (10.9%)	34 (13.1%)	51 (14.1%)
Yes	536 (86.3%)	155 (89.1%)	125 (88.0%)	158 (81.0%)	98 (89.1%)	225 (86.9%)	311 (85.9%)
Missing	5	1	0	3	1	1	4
3rd trimester							
No	96 (15.5%)	23 (13.3%)	21 (14.8%)	39 (20.0%)	13 (11.8%)	37 (14.3%)	59 (16.3%)
Yes	524 (84.5%)	150 (86.7%)	121 (85.2%)	156 (80.0%)	97 (88.2%)	222 (85.7%)	302 (83.7%)
Missing	6	2	0	3	1	1	5

2.2.2.4 Maternal Questionnaire

The questionnaire also collected basic information on maternal demographics, birth characteristics, and other risk factors such as fertility treatment, medications during pregnancy, pregnancy characteristics and family history of cancer.

2.2.3 Genetic Exposure

2.2.3.1 DNA collection and extraction

DNA was collected from the child, if still alive, and biologic mother and father. Oragene saliva collection kits were sent to the mother after the consent form was received. Adult kits included a small bottle of mouthwash, a pre-labeled specimen cup, a plastic bag, instructions, and a mailer with return postage. For the child, a cytobrush kit was included. For deceased cases, with parental consent, stored biologic samples were requested from the COG Neuroblastoma Biology Protocol, which banks serum, pretreatment whole blood, and paraffin-embedded or fresh-frozen tumor tissue.

DNA extraction and amplification was completed by the UNC Biospecimens Processing Facility. The DNA from the cytobrush and the mouthwash kit was extracted with a magnetic-bead capture method on the MSMI robotic system (PerkinElmer). All samples extracted were quantitated with Applied Biosystems® TaqMan® RNase P Detection kit for cytobrushes kits and the Quant-iT™ PicoGreen® dsDNA Assay Kit from Molecular Probes by Life Technologies for mouthwash kits. For genotyping, any DNA concentration below 35 ng/ µL was concentrated using the Zymo Research: gDNA Clean & Concentrator Kit. After this concentration, the sample was re-quantitated using the TaqMan® RNase P Detection kit.

2.2.3.2 Genotyping

Genotyping was performed on 1,536 single nucleotide polymorphisms by UNC's Mammalian Genotyping Core Facility on the GoldenGate Assay using the Illumina BeadStation 500GX Genetic Analysis System.[310] Allelic discrimination was based on allele-specific primer extension followed by ligation. GoldenGate also included sample-dependent, sample-independent and contamination checks to ensure high quality including checks of allele-specific extension, gender, first hybridization, PCR uniformity, extension gap, and second hybridization.

2.2.3.3 Candidate genes

Candidate genes (

) were selected from the vitamin A, choline and folate transport and metabolism as described in 1.5 Literature on Vitamin Pathways. Genes were selected based on evidence in the literature that they were related to the transport and metabolism of vitamin A, folate or choline. Genes with prior evidence for biologic or epidemiologic relationship with birth defects and cancer were given priority. Additionally, a few vitamin A target genes that are related to neuroblastoma were also selected.

Haplotype tagging SNPs with a minor allele frequency greater than 5% were selected 20kb upstream to 10kb downstream from the candidate gene. Genotyping error rates are higher at lower frequencies and the power to detect effects is drastically reduced.[311] Since NENA is predominately European American, TAGster[312] with the greedy algorithm was used to capture haplotype tagging SNPs (minor allele frequency $\geq$ 5%) that tag SNPs in high linkage disequilibrium (LD; $r^2 \geq 0.8$) in Hapmap 3 release III CEU population. Additional candidate SNPs were chosen based on consistent epidemiologic literature suggesting an association with

birth defects or cancer. Since the case-parent triad design is not subject to confounding by population stratification, ancestry informative markers were not included. A total of 94 genes were selected and 1,536 SNPs were genotyped (

).

To assist in quality control, control samples were included within each plate of sample. A Centre de l'Étude du Polymorphisme (CEPH) family trio and duplicates were included on each plate to identify apparent violations of Mendelian inheritance and assess genotyping consistency. Poorly genotyped SNPs were identified based on poorly defined clusters in the intensity data, poor genotyping success rates, and Mendelian or genotyping inconsistencies. SNPs that failed genotyping quality control were excluded from analysis.

Table 7. Candidate gene list

	Gene	Number TagSNPs	Number Candidate SNPs	Total
Vitamin A	*ADH1A*	8	0	8
	ADH4	1	0	1
	ADH7	23	0	23
	ALDH1A1	18	0	18
	ALDH1A2	14	0	14
	ALDH1A3	8	0	8
	ALDH8A1	8	0	8
	BCMO1	22	0	22
	BCO2	13	0	13
	CEL	6	0	6
	CES1	6	0	6
	CRABP1	8	0	8
	CRABP2	12	0	12
	CYP26A1/CYP26C1	1	0	1
	CYP26B1	13	0	13
	DGAT1	1	0	1
	ISX	26	0	26
	LRAT	7	0	7
	PNLIP	4	0	4
	RARA	6	0	6
	RARB	11	0	11
	RARG	12	0	12
	RBP1	12	0	12
	RBP2	6	0	6
	RBP3	13	0	13
	RBP4	15	0	15
	RDH1	11	0	11
	RDH5	1	0	1
	RXRA	24	0	24
	RXRB	9	0	9
	RXRG	36	0	36
	STRA6	14	0	14
	TTR	3	0	3
Folate/Choline	*AHCY*	2	0	2
	ALDH1L1	4	0	4
	AMT	3	0	3
	ATIC	11	0	11
	BHMT	7	5	12

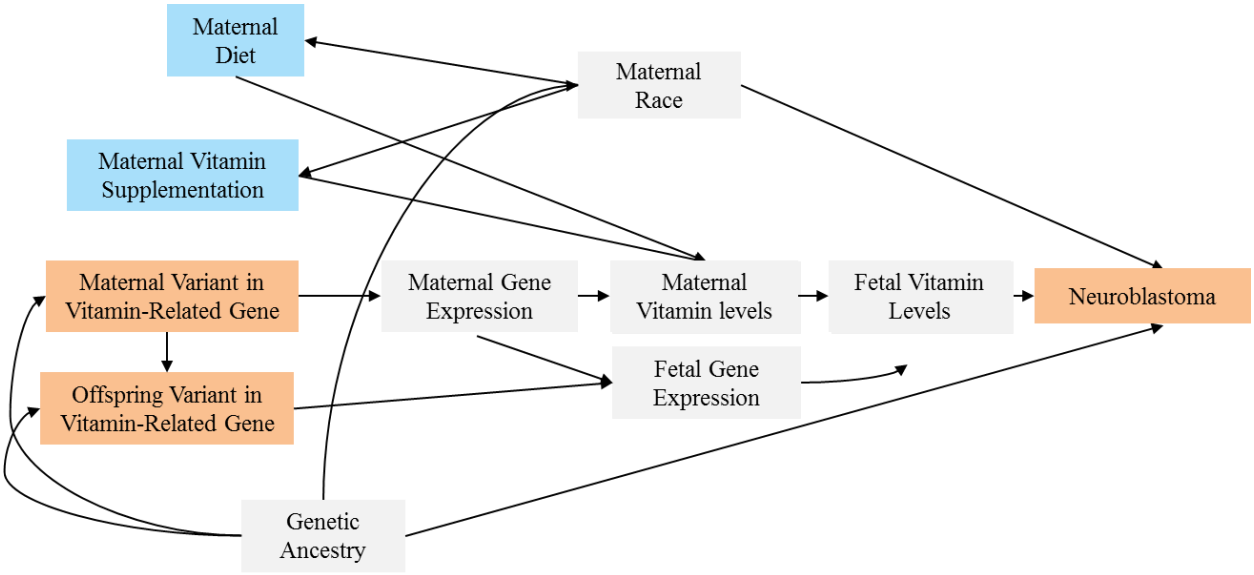
Gene	Number TagSNPs	Number Candidate SNPs	Total
BHMT2/DMGDH	25	0	25
CBS	19	6	25
CEPT1	15	0	15
CHDH	14	0	14
CHKA	1	0	1
CHKB	11	0	11
CHPT1	13	0	13
CTH	14	0	14
DHFR	5	7	12
DNMT1	6	0	6
DNMT3A	22	0	22
DNMT3B	16	0	16
FOLH1	8	0	8
FOLR1	2	1	3
FOLR2	3	2	5
FOLR3	9	0	9
FPGS	3	0	3
FTCD	24	0	24
GART	7	0	7
MAT1A	22	0	22
MAT2A	5	0	5
MAT2B	1	0	1
MTHFD1	17	7	24
MTHFD1L	15	0	15
MTHFD2	4	3	7
MTHFD2L	12	0	12
MTHFR	11	8	19
MTHFS	24	0	24
MTR	5	21	26
MTRR	18	8	26
NOS3	14	0	14
PCYT1A	21	0	21
PEMT	17	1	18
PLD1	14	0	14
PLD2	12	0	12
SARDH	43	0	43
SHMT1	7	1	8
SHMT2	7	0	7
SLC19A1	1	8	9
SLC22A2	22	0	22

	Gene	Number TagSNPs	Number Candidate SNPs	Total
	SLC22A3	24	0	24
	SLC22A4	16	0	16
	SLC22A5	1	0	1
	SLC44A1	11	0	11
	SLC44A2	1	0	1
	SLC44A3	45	0	45
	SLC44A4	14	0	14
	SLC44A5	42	0	42
	SLC46A1	5	0	5
	SLC5A7	19	0	19
	TCN2	18	0	18
	TYMS	19	4	23
Other	*RET*	19	0	19
	ZNF423	33	0	33

2.2.4 Covariates

Figure 8 is a causal diagram (or directed acyclic graph) between maternal and offspring variants and neuroblastoma.[313] Since there is not a factor that that temporally occurs before the maternal variant, with the exception of genetic ancestry, nothing is associated with the maternal SNP without being on the causal path. Additionally, since the case-parent triad analyzes the transmission of alleles from the parents to the child without a control group, adjustments for covariates are not needed.

Figure 8. Causal diagram. Blue is the "environmental" variable and orange represents the exposure and outcome



2.2.4.1 Genetic Ancestry

Genetic ancestry can lead to spurious results through population stratification in case-control studies. This results from differing allele frequencies and risks of disease across subpopulations (or ancestries) rather than due to causal associations with the disease.[314] This bias is particularly a concern in recently admixed populations such as Hispanic Americans or African Americans, but can also be present in European Americans.[315] However, this source of bias is inherently controlled for in a case-parent triad design since the analysis is conditional on parental genotypes (section 2.3.2 Offspring Genetic effect). However, for maternal genetic effects, if mating is selective with respect to the SNP and there could be bias because the father is serving as control for the mother.

2.2.4.2 Covariate description

Table 6 describes the participants who have completed the questionnaire by risk-classification and offspring age of diagnosis less than 1 year and greater than or equal to 1 year. Most mothers in this sample are European Americans, which is expected since neuroblastoma is most commonly diagnosed in European Americans. Additionally, similar to what is seen in SEER, there are more male than female children diagnosed with neuroblastoma. There are more deceased cases in the high-risk classification and cases greater than 1 year of age.

2.3 Analysis

There were three main analytic goals for the vitamin A, folate and choline genetic pathways. 1) Estimate the association of the offspring genotypes and the maternal genotypes 2) Analyze offspring genotypes and the maternal genotypes within strata defined by COG neuroblastoma risk-classification and offspring age at diagnosis 3) Determine if there is gene-environment interaction between the maternal and offspring genetic variants and the maternal vitamin consumption

2.3.1 Genotyping Quality Control

SNPs that had a call rate less than 95% were excluded from analysis. Individuals with gender discrepancies that could not be resolved (i.e. sample swap within family between mother, father and child) and had a genotyping rate less than 95% were also excluded. After these exclusions, the CEPH trio results were compared to their known genotypes to assess genotyping accuracy.

Initial data description consisted of the estimation of allele frequencies separately for the parents and the cases by racial/ethnic groups. Departures from Hardy-Weinberg equilibrium (HWE) were assessed for the European American race group with chi-square tests in the parents

with SAS 9.4. SNPs that failed HWE at a false discovery rate significance level < 0.02 were flagged, but not excluded. Mendelian errors were also assessed for each trio using PLINK v1.07. Relatedness was assessed for each trio through measures of identity by descent, alleles that share the same parental origin, with all alleles. The proportions of zero, one, or two alleles that are identical by descent are denoted by the notations P(Z=0), P(Z=1), and P(Z=2), respectively. A combined measure, $\hat{\pi} = P(Z = 2) * 0.5(P(Z = 1))$, can be used to assess relatedness. A $\hat{\pi}$ was calculated for each mother-child, father-child and mother-father pair in the trios. Within each trio, the parents were expected to have $\hat{\pi} < 12.5\%$, which is less than third-degree relatives, and for parent-child pairs a $\hat{\pi} \cong 0.5$ would expected. Reported fathers who are found not to be the biological father were excluded from further analysis.

2.3.2 Offspring Genetic effect

Genetic effects for the offspring genotype was evaluated using the log-linear model.[19] Although the transmission disequilibrium test (TDT) is the most common method for assessing genetic effects in case-parent triads, the log-linear model is comparable in terms of power, type 1 error, and robustness to population stratification, but allows estimation of genotype offspring and maternal risks ratios and assessment of gene-environment interaction and full and unbiased incorporation of triads that are incomplete due to missing paternal genotypes.[316]

Case-parent triads were classified according to the number of variant alleles carried by the mother (M), father (F) and child (C), resulting in a 15-cell multinomial distribution (Table 8), where variant alleles were defined as the allele with the lower minor allele frequency within the population. Hardy Weinberg equilibrium is not required for the valid application of log-linear models. Column 2 show the distribution under HWE, in which *p* is the proportion of the population with the variant allele. Column 3 shows the distribution of allele frequencies not

under HWE in the population, in which μ, a marker for the mating types, allows full stratification on parental mating type and confers robustness against population stratification. In the study sample, because triads were selected based on the disease occurrence in the offspring, the multinomial distribution is distorted by the risk ratios (R_1, R_2) (Table 8, Column 4). Two inherited copies of a variant allele increase the offspring risk by a factor of R_2 (risk ratio for 2 variant alleles) and one copy increases it by a factor of R_1 (risk ratio for 1 variant allele). Here mating symmetry is assumed, meaning that for couples in the source population M = 1 and F = 2 is as frequent as M = 2 and F = 1. If there are no maternally-mediated genetic effects, then under this log-linear model the expected count for each cell in the multinomial distribution can be written as

$$\ln\left[E\left(n_{M,F,C}\right)\right] = \gamma_j + \beta_1 I_{(C=1)} + \beta_2 I_{(C=2)} + \ln(2)\, I_{(M=F=C=1)} \qquad (1)$$

where the index j corresponds to the mating type, and where $I_{(\text{comparison statement})} = 1$ when the comparison statement is true and 0 otherwise.[19] This can be modified for a dominant model ($\beta_1 = \beta_2$) or a recessive model ($\beta_1 = 0$).[19] The multinomial likelihood can be maximized with Poisson regression software available in SAS. R_1 and R_2 can then be estimated by exponentiating β_1 and β_2, respectively. 95% confidence intervals can be calculated as

$$95\%\ CI = \left(e^{(\beta - 1.96 * Standard\ Error)}, e^{(\beta + 1.96 * Standard\ Error)}\right) \qquad (2)$$

All family-based models, including the log-linear model, must assume Mendelian transmission of alleles. Since there are no controls in this analysis, the null background is discerned from the parental genotypes under the assumption of Mendelian inheritance. Disruption of Mendelian inheritance at a particular locus, for example if homozygotes for the variant allele do not survive, would lead to results where two alleles appear to confer lower risk

than one allele. On the other hand, such an allele would be very quickly selected out of the population so that scenario is not a plausible one.

Table 8. Mating types and frequencies in case-parent triad

Mating type	Population Frequencies		Case-parent Triad Frequencies*
M,F,C	In HWE	Without HWE	
2,2,2	p^4	μ_1	$R_2\mu_1$
2,1,2	$p^3(1-p)$	μ_2	$R_2\mu_2$
1,2,2	$p^3(1-p)$	μ_2	$R_2\mu_2$
2,1,1	$p^3(1-p)$	μ_2	$R_1\mu_2$
1,2,1	$p^3(1-p)$	μ_2	$R_1\mu_2$
2,0,1	$p^2(1-p)^2$	μ_3	$R_2\mu_3$
0,2,1	$p^2(1-p)^2$	μ_3	$R_1\mu_3$
1,1,2	$p^2(1-p)^2$	μ_4	$R_2\mu_4$
1,1,1	$2p^2(1-p)^2$	$2\mu_4$	$2R_1\mu_4$
1,1,0	$p^2(1-p)^2$	μ_4	μ_4
1,0,1	$p(1-p)^3$	μ_5	$R_1\mu_5$
0,1,1	$p(1-p)^3$	μ_5	$R_1\mu_5$
1,0,0	$p(1-p)^3$	μ_5	μ_5
0,1,0	$p(1-p)^3$	μ_5	μ_5
0,0,0	$(1-p)^4$	μ_6	μ_6

* μ is numerically distinct from the population frequencies without HWE
M: Mother; **F**: Father; **C**: Child; **HWE**: Hardy Weinberg Equilibrium; $\mathbf{R_1}$: Risk ratio for 1 allele $\mathbf{R_2}$: Risk ratio for 2 alleles, compared with offspring having no copies.

2.3.3 Maternal Effect

The log-linear model can be expanded to test for maternal effects. As was true for the offspring genotype, maternal effects can also be estimated.[317] If there is a deleterious effect on the fetus due to a variant maternal allele then mothers will tend to have more copies than fathers among case families. This means that the distribution of the alleles will be biased by the maternal risk ratio S_1 and S_2 for 1 risk allele and 2 risk alleles, respectively. Table 9 shows the distributions of the case-parent triads in terms of S_1 and S_2.

Table 9. Mating types and frequencies in case-parent triad for maternal effects

Mating type	Case-parent Triad Frequencies	
M,F,C	Maternal Effect	Maternal and Child Effect
2,2,2	$S_2\mu_1$	$R_2S_2\mu_1$
2,1,2	$S_2\mu_2$	$R_2S_2\mu_2$
1,2,2	$S_1\mu_2$	$R_2S_1\mu_2$
2,1,1	$S_2\mu_2$	$R_1S_2\mu_2$
1,2,1	$S_1\mu_2$	$R_1S_1\mu_2$
2,0,1	$S_2\mu_3$	$R_2S_2\mu_3$
0,2,1	μ_3	$R_1\mu_3$
1,1,2	μ_4	$R_2\mu_4$
1,1,1	$2S_1\mu_4$	$2R_1S_1\mu_4$
1,1,0	$S_1\mu_4$	$S_1\mu_4$
1,0,1	$S_1\mu_5$	$R_1S_1\mu_5$
0,1,1	μ_5	$R_1\mu_5$
1,0,0	$S_1\mu_5$	$S_1\mu_5$
0,1,0	μ_5	μ_5
0,0,0	μ_6	μ_6

M: Mother F: Father C: Child

The expected count for each cell in the multinomial distribution can be modeled as

$$\ln\left[E\left(n_{M,F,C}\right)\right] = \mu_j + \alpha_1 I_{(M=1)} + \alpha_2 I_{(M=2)} + \ln(2)\, I_{(M=F=C=1)}, \quad (3)$$

where the index j corresponds to the mating type, and where $I_{(\text{comparison statement})} = 1$ when the comparison statement is true and 0 otherwise. Similar to case genotype model, S_1 and S_2 then can be estimated by exponentiating $\alpha_1$and α_2, respectively. If the triad data are complete, the estimations of maternal effects and offspring genotype effects are independent of each other despite the correlation between the mother and offspring genotypes.

In practice, some triads are usually incomplete and *a priori* it is unknown if the candidate gene has a maternally mediated effect or an offspring genetic effect. Since both scenarios are possible, the model can be altered to include both terms as

$$\ln\left[E\left(n_{M,F,C}\right)\right] = \mu_j + \beta_1 I_{(C=1)} + \beta_2 I_{(C=2)} + \alpha_1 I_{(M=1)} + \alpha_2 I_{(M=2)} + \ln(2)\, I_{(M=F=C=1)}, \quad (4)$$

where again the index j corresponds to the mating type, and where $I_{(\text{comparison statement})} = 1$ when the comparison statement is true and 0 otherwise. This model allows for the simultaneous evaluation of the maternal and offspring genetic effect. A likelihood ratio test can also be used to determine if the offspring genotype carries any predictive value after adjusting for the maternal genotype or vice versa. 95% confidence intervals can be calculated by equation 2 for the offspring effect and by substituting α for β.

In addition to the assumption of Mendelian inheritance, this model requires stronger assumptions than the test the offspring genetic effect. Since this model compares the allele counts in the father with the allele counts in the mother, this model assumes the symmetry of allele counts that does not need to hold for the test of the offspring genetic effects only.

2.3.4 Gene-Environment Interaction

The model of gene-environment interaction is just an extension of the offspring genetic only model, only there is term for the interaction of the gene and the environment. The expected count for a binary exposure is modeled as

$$ln\left[E\left(n_{M,F,C,E}\right)\right] = \mu_j + \delta_{je} I_{(E=e)} + \beta_1 I_{(C=1)} + \beta_2 I_{(C=2)} + \alpha_1 I_{(M=1)} + \alpha_2 I_{(M=2)} \beta_c I_{(C=c)} + \eta_{ce} I_{(C=c)} I_{(E=e)} + \gamma_{me} I_{(C=c)} I_{(M=m)} + ln(2)\, I_{(M=F=C=1)}, \quad (5)$$

where j indexes the mating types, $\mu_j + \delta_{je}$ are the corresponding stratum parameters of different levels of exposed triads and $\delta_{j0} = 0$ for each j. The $\beta_1$and β_2 are natural logarithms of the unexposed offspring genotype risk ratio associated with C=1 and C=2. The $\beta_1 + \eta_{1e}$ and $\beta_2 + 2 * \eta_{2e}$ are the natural logarithms of the exposed offspring genotype risk ratio of the C=1 triads and C=2 triads. The $\alpha_1$and α_2 are natural logarithms of the maternal genotype risk ratio associated with M=1 and M = 2 of the unexposed triads. The $\alpha_1 + \gamma_{me}$ and $\alpha_2 + 2 * \gamma_{me}$ are the natural logarithms of the maternal genotype risk ratio of the C=1 and the E=e triads and C=2 and

the E=e triads. If there is a dichotomous variable, then there will be 4 risk ratios for the offspring genotype and 4 risk ratios for the maternal genotype, or two for each level of the exposure. The 95% confidence interval for those who are unexposed will be equation 2. The 95% confidence intervals for those who are exposed will be

$$95\%\ CI(RR_{ce}) = \left[e^{(\beta_c+\eta_{ce})-\sqrt{Var(\beta_c)+var(\eta_{ce})+2cov(\beta_c,\eta_{ce})}}, e^{(\beta_1+\eta_{11})+\sqrt{Var(\beta_c)+var(\eta_{ce})+2cov(\beta_c,\eta_{ce})}}\right]. \quad (6)$$

This can also be calculated by separating the data into the two strata and applying (2) to each. Similar to the child genotype model, the gene-environment interaction model also assumes Mendelian transmission, but within each level of the exposure. Additionally this model also assumes conditional independence, which states conditional on parental genotypes, an individual's exposure status is independent of their genotype. For example, this assumption would be violated if neither the genotype nor the exposure is associated with the outcome, but if fetal inheritance of the variant allele somehow caused increased maternal exposure. This would not be a problem for the fetal gene-environment effects, but for maternal effects the maternal race may need to be adjusted for in the model, but only if there are many biracial couples. Alternatively, the model can be restricted to same-race parents to see if the results are similar.

2.3.5 Missing Paternal Genotype

Parent-child dyads can also be included in the analysis. Missing paternal genotype are accounted for by maximizing the observed data log-linear likelihood using the expectation maximization (EM) algorithm.[20] The EM algorithm maximizes the observed-data likelihood by fractionally assigning incomplete triads into their data-compatible cells on the basis of the current parameter estimates, and then repeating the calculations iteratively up to convergence and maximization of the likelihood. A crucial assumption is that the missingness is non-

informative, meaning that missingness is conditionally independent of the paternal genotype, conditional on the observed mother-child genotype. This assumption can be violated if missingness is related to race, but one can potentially deal with this issue by stratifying on race and doing the maximizations of mating type parameters within racial categories.

2.3.6 Stratifying by Risk-Classification and Offspring Age at Diagnosis

Since there is evidence that these subtypes are neuroblastoma may be different diseases rather than progressions of the same disease,[1] the offspring genetic and maternal genetic model was stratified for each neuroblastoma risk group defined by COG (see section1.2.4 Neuroblastoma Risk-Classifications). Similarly, the model was stratified by infant versus childhood cases. Infant cases are those that are less than 1 year of age at diagnosis and childhood cases are those greater than or equal to 1 year of age. Unlike risk-classification, age is available for all cases, which allows greater power for detecting an effect. Additionally, cases that are diagnosed after 1 year of age tend to have more severe outcomes, although they might have similar morphologies.[23]

2.3.7 Definition of Genetic Model and Environment

The model was fit log-additively for the maternal and offspring genetic effects. For the gene-environment model, the main genetics effects were fit co-dominantly, but the interaction term was modeled log-additively, to improve power.

Gene-environment interaction was modeled in three ways. First, the vitamin information from the FFQ was used. Second, a dichotomous variable for any prenatal/ multivitamin use 1 month before pregnancy was used. Lastly, we created a "total" exposure grouping for folate, folic acid and vitamin A by grouping women into two categories (sufficient and insufficient intake). Women with either greater than the 33rd percentile nutrient from diet or taken a prenatal

or multivitamin 1 month pre-pregnancy were classified as sufficient intake. Women with less than the 33rd percentile and did not take a prenatal or multivitamin 1 month pre-pregnancy were classified as insufficient.

The nutrients of interest are dietary maternal vitamin A, folate, and choline levels. Total choline, total folate dietary folate equivalent (DFE), folic acid and vitamin A retinol activity equivalent (RAE) were nutrients used from the FFQ. These values were dichotomized at the 25th percentile for gene-environment analysis.

A dichotomous variable based on dietary recommendations was also used. [18,318,319] Recommendations for folate and vitamin A are from the Recommended Dietary Allowances (RDA). Choline is based on Adequate Intake – a commonly used recommendation level in the absence of RDA values.[320] Folic acid is does not have a recommended amount, but the Institute of Medicine recommends women who are trying to get pregnant consume 400 mg/day folic acid in addition to a varied diet. The recommended cutoffs are as follows:

a. Folic acid for women who may get pregnant is 400 μg
b. Folate for women who may get pregnant is 600 μg dietary folate equivalents
c. Vitamin A for women is 700 μg retinol activity equivalents per day (No recommendation is given for women trying to get pregnant
d. Choline for women above the age of 19 years is 425 mg/day.

2.3.8 Replication

Dr. John Maris and colleagues at the Children Hospital of Philadelphia (CHOP) previously conducted a genome-wide association (GWA) case-control study with 2,101

neuroblastoma cases and 4,202 healthy controls of European American ancestry. This study was used to as a replication study for the offspring results in NENA.

Detailed information on this study can be found elsewhere.[8] Briefly, the cases were diagnosed with neuroblastoma or ganglioneuroblastoma and identified through the Neuroblastoma Bio-repository for specimen collection at the time of diagnosis. The controls with no known medical disorder were recruited from multiple sites within the CHOP Health Care Network, including four primary care clinics and several group practices and outpatient practices that included well child visits. At least 1.5 µg of high quality DNA was extracted from either a blood sample or bone marrow mononuclear cells for cases and blood samples of the controls. Based on genome-wide IBS estimates for all pairwise comparisons among all case and control subjects, they identified two matched controls for each case. Since both CHOP and NENA recruited cases from the same population, cases that were enrolled in NENA were excluded from the CHOP sample, resulting in 2,052 cases and 4,104 controls.

Imputation was performed with IMPUTE2 on all GWA data using the world-wide 1000 Genomes Project Phase 1 interim data as reference (June 2011 release). Detailed information on the imputation can be found elsewhere.[8] All SNPs were tested for association with neuroblastoma using the under the additive model in SNPTEST. Associations with for all neuroblastoma cases as well as by risk-classification and age at diagnosis were provided to NENA.

SNPs that are in both the NENA dataset and the CHOP dataset were included in the replication (N=1173) and 66.6% of these SNPs were genotyped. The CHOP SNPs were adjusted with false discovery rate and any SNP <0.2 was considered significant.

2.3.9 Analytical Considerations

2.3.9.1 Correction for Multiple Testing

To account for multiple testing a false discovery rate (FDR) Q-value was calculated instead of p-values. We considered any FDR Q-values < 0.2 as significant and as meriting additional follow-up. The FDR is less stringent than other tests for multiple corrections and thus provides a more useful approach for identifying genetic contributions to risk.[321]

2.3.9.2 Bias in measuring pregnancy diet and exposures

There is a potential for differential accuracy of recall since mothers had to recall exposures during and pre-pregnancy, which means mothers with older children, and generally more severe cases of neuroblastoma, will have longer to recall. Few studies have looked at maternal recall of medications during pregnancy and birth characteristics postpartum, but findings suggest that most birth characteristics and medications are accurately recalled by the mother with little difference by case or control status.[322,323]

NENA also did not collect dietary information from the pregnancy, but rather collected current dietary data and then asked about dietary changes during pregnancy compared to current diet. Since vitamin consumption was split into quartiles and recommended values and the comparisons are relative to other women within the study, we presume that few women would shift vitamin quartiles. There is also evidence that consumption of many foods does not change after pregnancy,[306,307,324]

Additionally, sensitivity analyses were done shifting nutrients based on changes in diet due to pregnancy. We used the questions that asked about changes in diet during pregnancy and concentrated on fish and diary, since these two foods changed the most during pregnancy. Fish and dairy contribute to choline and dairy contributes to vitamin A. We didn't analyze folate

changes since most women derive folate from breads and these are generally stable though pregnancy. We calculated the average amount fish and dairy contributed to choline and dairy contributed to vitamin A in NENA mothers. We increased the average amount dairy contributed to choline and vitamin A among women who reported greatly increasing dairy during pregnancy. Similarly, we decreased choline the average amount fish contributed choline in NENA for women who reported they had greatly decreased fish consumption during the pregnancy. The nutrients were then re-dichotomized and the gene-environment interaction was re-fit.

2.3.9.3 Selection

The CCRN has good coverage of neuroblastoma cases in the US. According to Musselman et al., the coverage of CCRN when compared to expected values from SEER is 60% to 70% for children younger than 5 years. The proportions of expected cases under 1 year of age is 37%, which is very similar to the 41% found in NENA.[304] The proportions of neuroblastoma subtypes and cancer origins in NENA are very similar to that seen in data from SEER. Although there are limitations for using the CCRN, it remains the best method for obtaining cases of neuroblastoma within the United States.

In addition to enrollment in the CCRN, there are many levels of recruitment in NENA, which can further introduce loss and potential selection bias. However, since this is a case-parents study and the parents are providing the comparison group, any form of selection would have a small possible effect on the generalizability of the inference rather than the validity of the results.

2.3.9.4 Assumptions for a case-parent triads

Since the underlying basis for case-parent triad studies is determining if observed data deviate from Mendelian expectations, the key assumption required for a valid analysis is the assumption of Mendelian transmission to offspring and that the proportions persist to the age in which cases are collected. Although deviations in Mendelian inheritance through biologic mechanisms are rare, it is possible that a variant is associated with survival, thus violating this assumption. For example, among children of parents who are both heterozygous, the ratio of offspring with 2, 1, and 0 copies of the variant allele would be 1:2:1. If a ratio of 4:2:1 were seen, deviation from this would be consistent with a recessive genetic risk of 4. However if this deviation were to occur because the variant is associated with survival rather than disease, the risk ratio estimate would be invalid. There is some evidence that the variants in this present study, such as *MTHFR* C677T and A1298C are related to survival,[325] but these studies are small and it is hard to determine if these variants are related to survival since most embryonic death occurs before the women knows she is pregnant. Additionally, the deviations that are present are very small and unlikely to affect the study.

2.4 Statistical Power

2.4.1 Genetic effect

All power calculations were done with QUANTO Version 1.2.4. There are 603 case-parent triads or parent-child dyads with DNA. Assuming an alpha of 0.001, this yields greater than 80% power to detect minimum risk ratios at 1.5 at a minor allele frequency (MAF) of 20% for a log-additive genetic effect (Table 10). The power is not greater than 80% for the detection of a risk ratio of 1.3 at a genotype prevalence of 30%. Previous GWA study analyses of neuroblastoma have found hits at that magnitude.[6] For a recessive genetic effect (two variant

alleles versus one or none), there is about 52% power to detect risk ratios above 1.7 and with a MAF of 30%. The dominant genetic effect (one or two variant alleles versus none) has power greater than 80% to detect risk ratios greater than or equal to 1.7 at a MAF of 20%. Research has shown that it is likely that these work in an additive fashion, where homozygotes for a variant have greater impairment of vitamin metabolism than those who are heterozygotes.[326]

Table 10. Power for offspring genetic effect

Genotype Prevalence	Risk Ratio	Study Power (N = 603)		
		Additive	Recessive	Dominant
10%	1.3	10.44%	0.34%	7.90%
	1.5	47.43%	0.92%	36.88%
	1.7	84.73%	2.13%	73.62%
20%	1.3	26.84%	1.44%	15.50%
	1.5	81.91%	6.40%	59.40%
	1.7	98.88%	18.36%	90.85%
30%	1.3	39.32%	4.16%	17.51%
	1.5	92.19%	21.02%	62.64%
	1.7	99.82%	51.92%	91.86%

Assumptions: $\alpha = 0.001$

2.4.2 Stratification by Risk-Classification and Age

Assuming the same numbers that were displayed in Table 6 for risk group and age group, there is less than 80% power to detect risk ratios up 1.7 for all risk-groups (Table 11). There is better power by age group since this is available for all cases, where there is power greater than 80% with a risk ratio of 1.7 and a MAF of 80% in cases greater than 1 year.

Table 11. Power for risk-classification and < 1 year and greater than or equal to 1 year of age

Genotype Prevalence	Risk Ratio	COG Risk-Group			Age Group	
		Low-Risk (N = 175)	Intermediate Risk (N = 142)	High-Risk (N = 198)	< 1 year (N = 260)	≥1 year (N = 366)
10%	1.3	1.41%	1.06%	1.68%	2.53%	4.40%
	1.5	6.03%	4.23%	7.47%	12.06%	21.85%
	1.7	16.71%	11.58%	20.67%	32.38%	52.82%
20%	1.3	3.21%	2.31%	3.93%	6.23%	11.35%
	1.5	15.23%	10.54%	18.88%	29.77%	49.34%
	1.7	38.68%	27.91%	46.16%	64.42%	85.37%
30%	1.3	4.81%	3.40%	5.94%	9.55%	17.41%
	1.5	22.55%	15.73%	27.68%	42.13%	64.73%
	1.7	51.94%	38.88%	60.31%	78.22%	93.81%

Assumptions: $\alpha = 0.001$

2.4.3 Gene Environment Interaction

There are 588 case-parent triads or parent-child dyads that have both DNA and questionnaire data. Assuming that the genetic risk ratio is 1.3 for an additive genetic effect, which is reasonable given the previous literature, and the environment risk ratio is 1.667 for those with low vitamin consumption, there is power greater than 80% to detect a joint gene-environment risk ratio above 2.2 (that is, among exposed individuals the effect of each copy of the variant is increased by a factor of 2.2) for a MAF of 30% (Table 12). Thus, the relative risk for an exposed carrier of one copy, assuming a (no interaction) multiplicative joint effect, would be 2.17. Under the detectable interaction alternative, the joint relative risk, comparing the exposed carrier of one copy to an unexposed non-carrier, would be 2.17*2.2=4.77.

Table 12. Power for gene-environment interaction

Genotype Prevalence	GXE Risk Ratio	Exposure Prevalence		
		20%	30%	40%
10%	1.8	14.32%	16.47%	15.33%
	2.0	26.24%	29.07%	26.59%
	2.2	40.42%	43.24%	39.20%
20%	1.8	35.22%	37.83%	34.10%
	2.0	56.78%	58.36%	52.47%
	2.2	74.77%	74.79%	67.94%
30%	1.8	48.99%	50.18%	44.34%
	2.0	71.72%	70.97%	63.28%
	2.2	86.57%	84.64%	77.02%

Assumptions: $\alpha = 0.001$, Genetic Risk Ratio = 1.3, Environment Risk Ratio =1.7, n = 588; GXE = Gene-environment interaction

2.5 Strengths and Limitations

Neuroblastoma is the second most common solid tumor diagnosed in children and the most common malignancy diagnosed in infants.[1] Due to the embryonic origins of neuroblastoma, it is likely that there is a strong genetic component of both the maternal genetics and the offspring genetics that is modified by the fetal environment.[1,68] NENA is the only study that is able to study both maternal genetic effects as well as gene-environment interaction with maternal pre-pregnancy and pregnancy vitamin consumption.

One strength of this study is the use of the case-parent triad, which prevents selection bias through recruitment of controls that are not from the study base or have a low response. Additionally, with key assumptions, we can validly estimate maternal effects and gene-environment effects. Also, case-control approaches are inevitably vulnerable to confounding of offspring genetics by maternal genetics, whereas those two causal mechanisms can be distinguished clearly using a case-parent design. In a rare disease setting like neuroblastoma, which requires recruiting cases North America-wide, population-based controls are difficult to recruit. Additionally, through the COG, DNA samples had been previously collected and stored

for deceased cases. The ability to genotype these "fast progessors" enabled us to study neuroblastoma as a whole rather than the cases that have survived. The case-parent triad also accounts for population stratification without additional genotyping, since the calculations are conditional on parental genotype.

The CCRN provides a good platform to accumulate neuroblastoma cases. NENA is the largest study of this rare childhood cancer that is able to look at gene-environment interactions. Since neuroblastoma is a rare disease and amassing cases is difficult, even within the context of the CCRN, hypothesis-driven candidate genes allow us to look at functionally relevant genetic variants without sacrificing power. The selected genes give good coverage of vitamin A, folate, and choline pathways that have *a priori* plausibility of a relationship with neuroblastoma.

This study has a few limitations as well. First there is a potential for measurement bias for maternal diet. Since we must use reported current diet from a FFQ, we relied on women's current diet to approximate her pre-pregnancy and early pregnancy diet. However, data was collected on the estimated amount of dietary change of certain foods due to pregnancy. This is the only study to look at the joint effects of maternal diet during pregnancy and the genetics of both the child and the mother. There are a few assumptions to the case-parent triad such as Mendelian inheritance and conditional independence of the exposure and the transmitted genotype, but these needed assumptions are less severe than the assumption that the controls are representative of the study base and that population stratification is adequately accounted for.

CHAPTER 3: AIM 1 RESULTS

Maternal and offspring variants in vitamin A-related genes and gene-environment interaction with vitamin A and neuroblastoma: A report of the Children's Oncology Group

3.1 Overview

Multivitamins and prenatal vitamin intake has been associated with decreased risk of neuroblastoma, a childhood cancer of the sympathetic nervous system. Retinoic acid is a chemical compound related to vitamin A that stimulates differentiation of neuroblastoma cells *in vitro*. 13-*cis*-retinoic acid has been used to reduce recurrence after treatment for high-risk neuroblastoma. We hypothesized that common variants in vitamin A-related genes are associated with risk of neuroblastoma and are modified by maternal vitamin A intake. The Neuroblastoma Epidemiology of North America (NENA) study recruited 563 case-parent sets through the Children's Oncology Group's (COG) Childhood Cancer Research Network. NENA used questionnaires to ascertain pre-pregnancy supplementation and estimate usual maternal dietary intake. We genotyped 463 SNPs related to vitamin A pathways, used a log-linear model to estimate log-additive child and maternal risk ratios and stratum-specific risk ratios for gene-nutrient interactions. We corrected for multiple testing using the false discover rate. In the overall study group, no offspring variants were significantly associated with risk of neuroblastoma. The maternal variant rs12442054 was significantly associated with overall decreased risk of neuroblastoma. After stratification by the COG prognostic risk-classification, nine offspring

SNPs (rs4842196, rs1229977, rs1045570, rs1007971, rs7139068, rs904092, rs3118523, rs7169439, and rs1465057) were significantly associated with the intermediate-risk neuroblastoma. Maternal rs6776706 and rs11103603 were also significantly associated with decreased risk of high-risk neuroblastoma and cases in which diagnosis was made at age less than 1 year, respectively. We found a maternal rs729147-vitamin A interaction when maternal vitamin A consumption was dichotomized at the Recommended Dietary Allowance. Our results suggest that some genetic variants involved in vitamin A may be associated with neuroblastoma. The significant maternal variants and their joint effects with maternal vitamin A intake, suggest a relationship between neuroblastoma and vitamin A.

3.2 Introduction

Neuroblastoma is an embryonal tumor arising from the neural crest and is the most common extracranial solid tumor in children.[1,2] Its incidence is slightly higher in males than in females (7.7 per million vs 6.9 per million).[327] Neuroblastoma has an embryonic origin, implying that the prenatal environment as well as offspring and maternal genetics are likely involved in its etiology. Genome-wide association (GWA) studies and studies of familial case have identified rare and common offspring germline variants associated with the risk of neuroblastoma.[6,328]

Previous epidemiologic studies have found evidence of an inverse association between maternal prenatal vitamin use and neuroblastoma,[10,11] suggesting that maternal pregnancy vitamin status may play a role in neuroblastoma development. Vitamin A in the form of beta-carotene is found in most prenatal vitamins and is required for many growth and developmental processes including embryonic neuronal differentiation and development.[12,13] When cultured neuroblastoma cells are treated with retinoic acid, a metabolite of vitamin A, they exhibit

decreased proliferation and improved differentiation.[14,15] Therefore, 13-*cis*-retinoic acid is clinically used to prevent the recurrence of disease after treatment for some cases of neuroblastoma.[170,171]

Due to the importance of vitamin A in neuronal development and differentiation as well as the epidemiologic associations between vitamin use and neuroblastoma, we hypothesized that common maternal and offspring SNPs in genes involved in vitamin A metabolism and transport are associated with neuroblastoma. Furthermore, we hypothesized that these variants are modified by maternal vitamin A intake through diet and prenatal vitamin supplementation. However, no studies have been conducted to evaluate gene-environment interaction with maternal intake of specific nutrients, such as vitamin A, or studied the effects of maternal genetic variants. The present study is the first to examine the risk of neuroblastoma and genetic variants involved in vitamin A processing and transport.

3.3 Methods

3.3.1 Study Sample

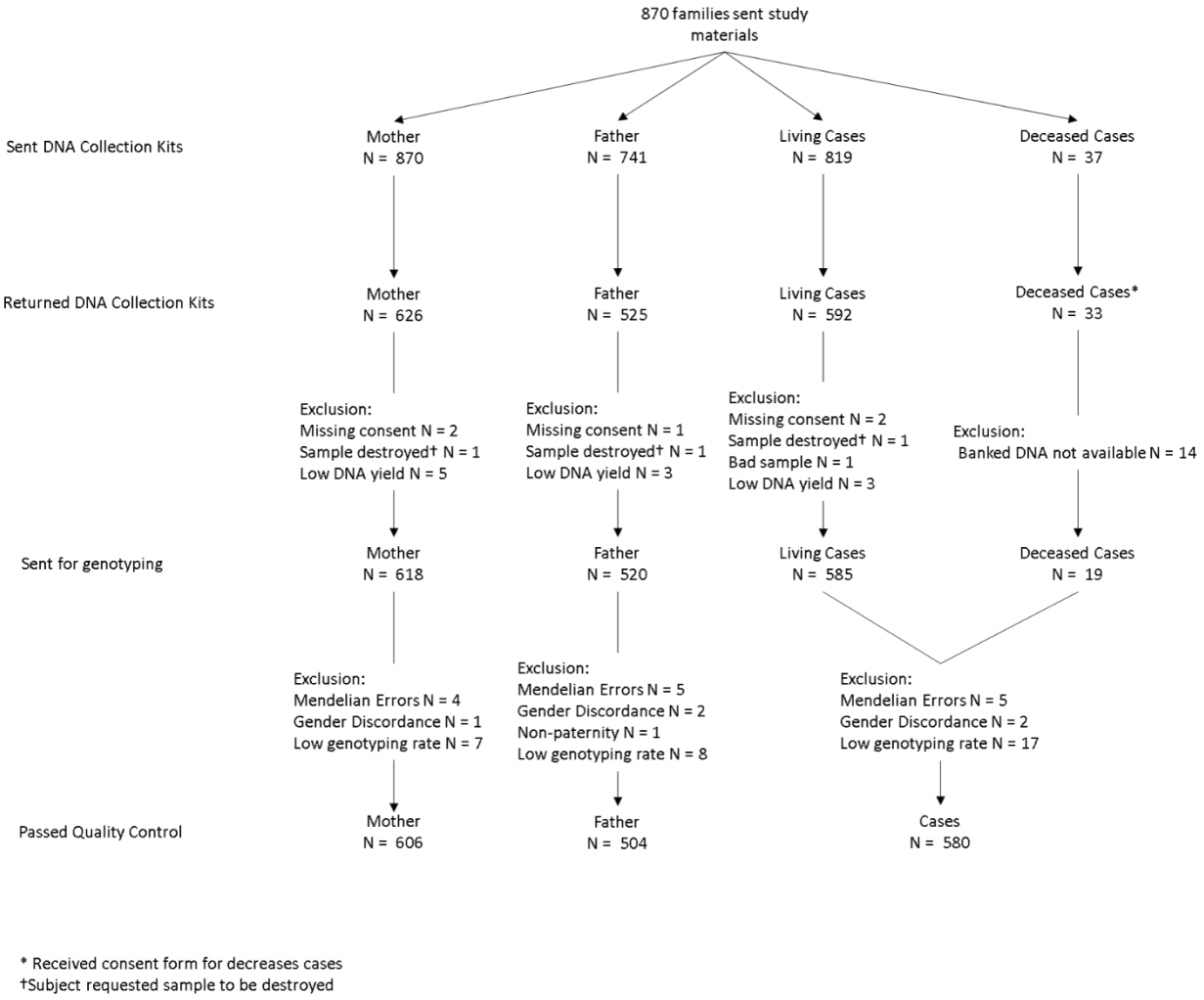
The Neuroblastoma Epidemiology in North America (NENA) study used a case-parent triad design to investigate gene and gene-environment interactions in the etiology of neuroblastoma. NENA recruited families who agreed for future contact and were registered in the Childhood Cancer Research Network (CCRN) a registry system of newly diagnosed cases maintained by the Children's Oncology Group (COG).[304]. To be eligible for NENA, cases had to have a primary diagnosis of neuroblastoma (including ganglioneuroblastoma but excluding ganglioneuroma) before the age of 6 years at a U.S. or Canadian COG institution from December 24, 2007 to July 31, 2013. The biologic mother was alive and willing to participate. The

University of North Carolina at Chapel Hill (UNC) Institutional Review Board approved this study.

NENA located and sent a recruitment packet to 1347 families located through the CCRN. Once the families agreed to participate (N = 870), we sent study materials containing a consent form, the maternal questionnaire, a mouthwash Oragene saliva spit tube collection kit for the parents, and an Oragene saliva sponge/disc kit for the child. If the child was deceased, communication was delayed by 15 months after date of death and a different protocol was used. A previously collected blood sample was obtained from the COG Neuroblastoma Bio-repository at the Children's Hospital of Philadelphia (CHOP).

We collected saliva samples from 626 biological mothers, 592 living children, 525 biological fathers and blood samples used for 19 deceased children (Figure 9). Questionnaires were returned by 630 mothers. However, two did not have a corresponding signed consent form and two were incomplete, which resulted in 626 completed questionnaires for analysis.

Figure 9. Flowchart of DNA collection, genotyping and genetic quality control for mothers, fathers and children in NENA**.**



3.3.2 Candidate Genes and SNP selection

Candidate genes were selected based on their role in the transport and metabolism of vitamin A. We tagged SNPs in the region between 20kb upstream to 10kb downstream from each gene.[312,329] We used TAGster with the greedy algorithm to capture haplotype tagging SNPs with a minor allele frequency ≥ 5% that tag SNPs in high linkage disequilibrium (LD; $r^2 \geq 0.8$) in the Hapmap 3 release III CEU population. Since the case-parent triad design is not subject to

confounding by population stratification, ancestry-informative markers were not included.[317] A 463 SNPs in 30 genes were selected for genotyping.

3.3.3 DNA collection and Genotyping

UNC Biospecimen Processing Facility performed the DNA extraction. Saliva samples from parents were collected in DNA Genotek's OGR-250 collections kits. Saliva from the child was also collected into these kits by the parents using 5 provided swabs to collect the saliva. DNA was extracted using the Perkin-Elmer's Chemagic MSMI magnetic-bead extraction robotic system and quality was assessed with Nanodrop Optical Density and quantitated with Applied Biosystems® Taqman® RNase P detection kit. A total of 498 triads, 99 mother-child dyads, 5 father-child dyads and 27 other (mother-father dyads and singleton cases) with DNA yields greater than 2 µg were sent for genotyping.

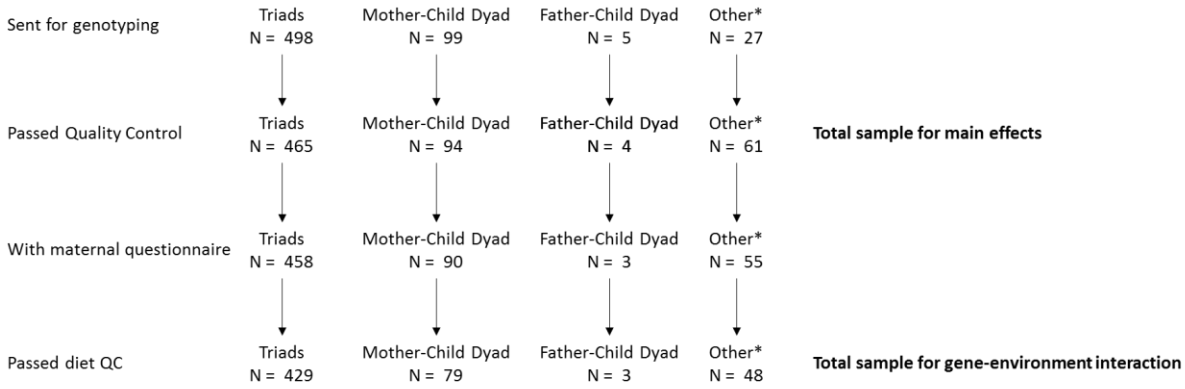
Genotyping was performed by UNC's Mammalian Genotyping Core Facility on the GoldenGate Assay using the Illumina BeadStation 500GX Genetic Analysis System. Allelic discrimination was based on allele-specific primer extension followed by ligation.

3.3.4 Genetic Quality Control

For quality control purposes, a Centre de l'Étude du Polymorphisme Humain (CEPH) family triad and blinded duplicates were included on each plate. SNPs with a genotyping call rate less than 95% were excluded. Individual genotypes for SNPs showing a lack of defined clusters in the raw genetic intensity data or showing apparent Mendelian errors in a particular family were treated as missing. A total of 427 vitamin A-related SNPs passed quality control. We assessed Hardy-Weinberg (HWE) equilibrium among parents who self-identified as white using chi-square tests in PLINK (v1.07) and flagged (n=5), but did not exclude, SNPs that failed HWE at a false discovery rate (FDR) significance level of < 0.2.[330,331]

Individuals with genotyping rates <95% or gender discrepancies were excluded. Relatedness was confirmed for each triad through measures of identity by descent and triads with unexpected relatedness were excluded. For example, when non-paternity was detected, the paternal data was excluded. A total of 465 triads, 94 mother-child dyads, 4 father-child dyads, 13 mother-father dyads and 48 singletons passed genetic quality control (Figure 10).

Figure 10. Flowchart for genetic and questionnaire quality control for triads and dyads.



*Other includes Mother-father dyads and singletons. There are 27 other initially and increase when either parents or children fail quality control.

3.3.5 Biological and Clinical Variables

Clinical and biologic characteristics of the tumor such as tumor genetics and stage were obtained from the COG Statistical and Data Center, which maintains data for cases enrolled in a COG clinical protocol. However, for 89 cases who were not enrolled in a COG protocol, these data were not available. The data also included the COG "risk-classification" using a schema that defined three prognostic risk-classifications: low-risk, intermediate-risk and high-risk. These risk-classifications are based on pathology, tumor stage, *MYCN* amplification, ploidy, and patient age dichotomized at 1 year.[43]

3.3.6 Maternal Vitamin Use

The mother's current and usual maternal diet during the preceding year was ascertained with the Dietary History Questionnaire, a self-administered semi-quantified food frequency questionnaire (FFQ). We assumed maternal usual diet in the last year approximates pre-pregnancy diet.

To address potential differences between "usual" diet and diet during pregnancy the questionnaire asked if women changed their diet relative to current diet in foods prone to change.[309] The mothers were asked if during pregnancy intake of these foods was "Much less than it is now", "Somewhat less than it is now", "Same as it is now", "Somewhat more than it is now", and "Much more than it is now".

Diet*Calc (version 1.5.0) was used to process the FFQs and to derive usual nutrient intake per day for previous last year. The nutrient and food group database was based on a compilation of national 24-hour dietary recall data from the National Health and Nutrition Examination Surveys (NHANES) conducted in 2001-02, 2003-04, and 2005-06 (http://riskfactor.cancer.gov/dhq2/database/). Certain foods not included in the original database were added by NENA staff in 100 gram amounts using the USDA database, standard release 24.

Mothers were also questioned about maternal dietary supplementation use 1 month pre-pregnancy and within each trimester of pregnancy. To aid in recall, an estimated conception date was provided; calculated by subtracting gestational age at delivery from infant birthdate. Since we are most interested in vitamin intake pre-pregnancy and early pregnancy, we focused on prenatal vitamin or multivitamin use 1 month pre-pregnancy.

3.3.7 Diet and Nutrient Classification

Maternal questionnaires that reported calories per day below the 5th percentile (N = 31; below 854.47 calories) or above the 97th percentile (N = 18; above 4508.75 calories) were excluded (Figure 10). Vitamin A is estimated in micrograms retinoic acid equivalents (μg RAE), which accounts for the differing bioactivities of retinol and provitamin A carotenoids. We explored two cutoffs for vitamin A: 25th percentile (460.94 μg RAE) and Recommended Dietary Allowance (RDA) for women of child-bearing age (700 μg RAE).[332]

Since we are unable to ascertain the formulations of the prenatal or multivitamins, we conducted a "total" exposure analysis by combining prenatal or multi-vitamin use and dichotomizing vitamin A from diet. Maternal total exposure was split into two groups: low intake and sufficient intake. Women with intake less than the 33rd percentile of vitamin A from diet and no prenatal or multivitamin supplementation 1 month pre-pregnancy were defined as "low intake". A woman was classified as "sufficient intake" if she has greater than the 33rd percentile of vitamin A from diet or took a prenatal or multivitamin supplement 1 month pre-pregnancy

3.3.8 Statistical Analysis

There were three main analytic goals: 1) estimate the genetic risk ratios (RRs) of the offspring and maternal genotypes; 2) estimate stratum-specific RRs by COG neuroblastoma prognostic risk-classification and offspring age at diagnosis; and 3) assess multiplicative maternal and offspring gene-environment interactions with maternal vitamin A. We used a codominant model to simultaneously assess the offspring and maternal log-additive genetic main effects and a log-additive model for gene-environment interaction.[317]

The null genetic background genotype is discerned from the parental genotypes under the assumption of Mendelian transmission in the source population, which allows us to estimate RRs without controls.[317] An additional assumption of mating symmetry in the source population is needed to estimate the maternally-mediated genetic association, since the maternal genotype frequencies. The maternal and offspring log-additive RRs were calculated simultaneously and are mutually adjusted. We can also account for missing paternal genotype with the expectation-maximization algorithm, which maximizes the observed-data likelihood by fractionally assigning incomplete triads into their data-compatible cells on the basis of the current parameter estimates, and then repeating the calculations iteratively up to convergence and maximization of the likelihood.[20]

The offspring and maternal genetic models were separately fitted for each prognostic COG risk-classification and offspring age at diagnosis dichotomized at 1 year with separate "mating type" and risk parameters allowed within each stratum. Offspring age at diagnosis was dichotomized into less than 1 year of age at diagnosis or "infant cases" and greater than or equal to 1 year of age or "childhood cases". This age dichotomy represents two different peaks in neuroblastoma age at diagnosis distribution.[333]

The gene-environment interaction model is an extension of the genetic only model with an additional term for the interaction of the offspring or maternal genotype and maternal vitamin intake.[21] This model enables estimation of genotypic RRs that can differ across levels of vitamin intake. The main genotype effects were coded co-dominantly, while the interaction term is fit log-additively to enhance power. If interaction terms were significant after multiple correction, then the interaction model was refit co-dominantly to characterize the interaction in a more flexible way.

To account for multiple comparisons, we corrected all p-values with the false discovery rate (FDR) and all reported results considered significant are FDR-corrected significant at Q-value less than 0.2.[334] . All estimated RRs will be presented in relation to the minor allele at the specified SNP.

3.3.9 Replication Study

We were able to provide replication for the results from offspring genotypes using genetic data and imputation from a previously conducted GWA offspring case-control study. Dr. John Maris and colleagues at the Children's Hospital of Philadelphia (CHOP) conducted GWA case-control study. Information on this study has been described elsewhere.[8] Briefly, the cases were identified through the Neuroblastoma Bio-repository maintained by the COG which collects germline and tumor specimens at the time of diagnosis. Controls with no known medical disorder were recruited from multiple sites within the CHOP Health Care Network that includes four primary care clinics and several group practices and outpatient practices. Population stratification was accounted for by adjusting for principle component scores. Since both the CHOP case-control and NENA studies recruited cases from the COG, there are an overlap of cases. Cases enrolled in NENA were excluded from the CHOP sample, resulting in 2,052 cases and 4,104 controls.

Because the platforms used for genotyping were not the same, analysis based on imputed genotypes was required. Imputation was performed on all CHOP GWA data with IMPUTE2 using the world-wide 1000 Genomes Project Phase 1 interim data as reference (June 2011 release).[335] The SNPs selected based on NENA (N=1173) were tested for association with neuroblastoma using SNPTEST under an additive model.[335] About a third of these SNPs were imputed in the CHOP replication sample. Odds ratios (ORs) for all neuroblastoma cases as well

as stratification by risk-classification and age at diagnosis were FDR-corrected. These results were then compared with the RRs from NENA.

3.3.10 Sensitivity Analysis

Many women increase dairy consumption during pregnancy and dairy is a large contributor of vitamin A, we performed sensitivity analyses adjusting vitamin A nutrient levels depending on self-reported change in dairy intake due to pregnancy. After this vitamin A intake adjustment, vitamin A was then dichotomized at the new 25th percentile and the gene-environment model was fit again. Additional methods are included in the supplementary methods.

Because women who breastfeed are advised to consume more calories, which alters nutrient intake additional sensitivity analyses were done excluding currently breastfeeding women.[336]

3.4 Results

We had genetic data for 465 triads and 98 dyads. Descriptive statistics for triads with genetic data are shown in Table 13. The mean age at diagnosis for the offspring was 1.7 years. As expected, the age at diagnosis differed across COG risk-classifications (p-value < 0.001) and the high-risk classification had the oldest age at diagnosis (2.6 years). Maternal age at birth was consistent across risk groups with the overall average maternal age of 29.8 years. There were more male (53.6%) than female cases in the study. This pattern of male excess was consistent across COG risk-classification groups except for the low-risk group (52.4% females). The predominant maternal race was white (84.8%). The median vitamin A maternal consumption was 672.21 μg RAE (Interquartile range: 458.18-978.16).

Table 13. Descriptive statistics for triads with genetic data

	Total		Low-risk		Intermediate-risk		High-risk		
	N	Mean (Std)	N	Mean (Std)	N	Mean (Std)	N	Mean (Std)	p
Maternal Age (Yrs)	606	29.7 (5.30)	186	29.4 (5.14)	146	29.5 (5.38)	204	30.0 (5.34)	0.591
Age at diagnosis (Yrs)	618	1.7 (1.43)	181	1.4 (1.40)	149	0.9 (0.87)	204	2.6 (1.20)	<0.001
	N	%	N	%	N	%	N	%	
Offspring gender									
Female	285	45.7	94	51.9	71	47.7	88	43.6	0.078
Male	339	54.3	87	48.1	78	52.3	114	56.4	
Maternal race									
White	513	84.7	140	79.6	120	82.2	174	87.9	0.042
Black	24	4.0	12	6.8	3	2.1	7	3.5	
Hispanic	36	5.9	16	9.1	11	7.5	7	3.5	
Other	33	5.5	8	4.6	12	8.2	10	5.1	
Missing	18	--	5	--	3	--	4	--	

Yrs: Years; **Std**: Standard Deviation; **p**: p-value

Among offspring, no SNPs were significantly associated with neuroblastoma (Appendix 1**)**. With stratification by COG-risk group, nine SNPs were significantly associated with intermediate-risk neuroblastoma (Table 14). These 9 SNPs are located near or in four genes: *RXRA*, *ADH1A*, *RARG*, and *ALDH1A2* (highest r^2=0.72).

Table 14. Offspring FDR-corrected significant SNPs results for intermediate risk group

		NENA					CHOP				
Gene	SNP	Effect Allele	Major Allele	RR (95% CI)	P-value	FDR Q-value	Effect Allele	Major Allele	OR (95% CI)	P-value	FDR Q-value
RXRA	rs4842196	C	A	1.97(1.32, 2.93)	0.001	0.185	--	--	--	--	--
ADH1A	rs1229977	T	C	0.48(0.31, 0.75)	0.001	0.185	C	T	0.87(0.67, 1.12)	0.278	0.933
RXRA	rs1045570	T	G	2.07(1.32, 3.24)	0.002	0.185	--	--	--	--	--
RXRA	rs1007971	G	C	1.94(1.27, 2.97)	0.002	0.185	--	--	--	--	--
RARG	rs7139068	T	A	0.40(0.21, 0.73)	0.003	0.185	--	--	--	--	--
ADH1A	rs904092	A	G	0.48(0.29, 0.78)	0.003	0.185	G	A	0.74(0.56, 0.98)	0.038	0.933
RXRA	rs3118523	G	A	2.09(1.27, 3.43)	0.004	0.185	--	--	--	--	--
ALDH1A2	rs7169439	A	G	2.75(1.39, 5.45)	0.004	0.185	--	--	--	--	--
RARG	rs1465057	C	T	0.37(0.19, 0.73)	0.004	0.185	C	T	1.10(0.75, 1.62)	0.609	0.933

CHOP: Children's Hospital of Philadelphia case control replication study; **RR**: Risk Ratio; CI: Confidence Interval; **OR**: Odds Ratio; --: Unavailable in replication study

Maternal rs12442054, selected for its proximity to *STRA6*, was significantly inversely associated with neuroblastoma overall (log-additive RR for each A allele: 0.61; 95% Confidence Interval (CI): 0.47, 0.79; Table 15). We also found significant results among the COG high-risk and infant cases. Maternal rs6776706 was significantly associated with decreased risk of high-risk neuroblastoma (log-additive RR for each A allele: 0.49; 95% CI: 0.33, 0.72). Each additional maternal copy of the C allele of rs11103603 conferred a risk ratio of 0.60 (95% CI: 0.45, 0.79) for infant neuroblastoma. Maternal results from all the SNPs can be found in Appendix 2**.**

Table 15. Maternal FDR-corrected significant SNPs results

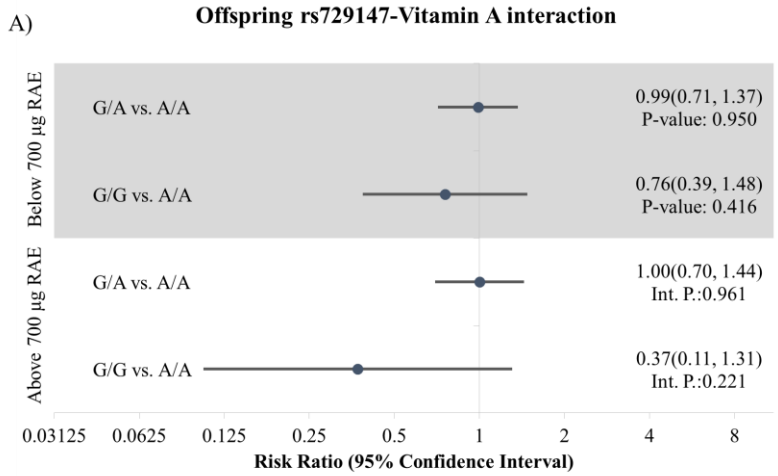
SNP	Gene	RR (95% CI)	P-value	Q-value
Overall				
rs12442054	STRA6	0.61(0.47, 0.79)	<0.001	0.076
High-Risk				
rs6776706	RARB	0.49(0.33, 0.72)	0.0004	0.161
Infants				
rs11103603	RXRA	0.6(0.45, 0.79)	0.0003	0.127

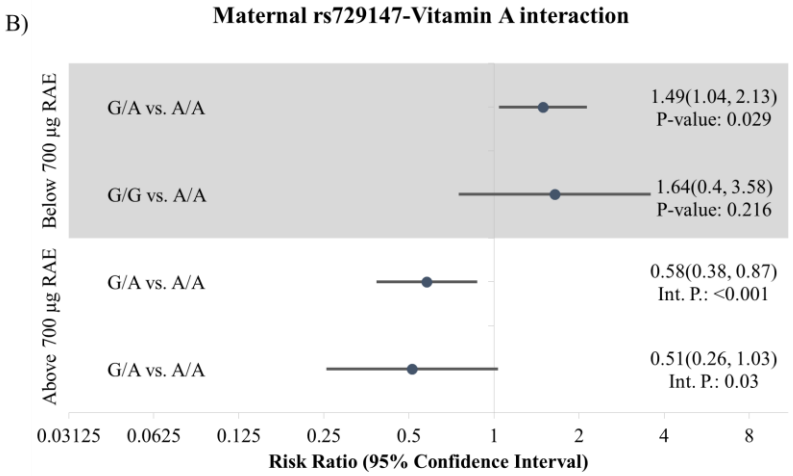
RR: Risk Ratio; **CI**: Confidence Interval

We found no significant gene-environment interactions with pre-pregnancy vitamin supplementation or when vitamin A dietary intake was dichotomized at the first quartile (results not shown) for either offspring or maternal genetic variants. We did find a significant additive interaction with maternal rs729147 (Figure 11) for maternal vitamin A intake dichotomized at the RDA (700 μg RAE) (Additive interaction p-value<0.001; Q-value=0.156). The interaction was modeled co-dominantly to allow more flexibility when estimating RRs. When maternal vitamin A intake was below the RDA, one G allele of maternal rs729147 was significantly associated with increased risk of neuroblastoma (RR G/A vs. A/A: 1.49; 95% CI: 1.04, 2.13). When maternal intake was above the RDA, one or two G alleles were associated with a

decreased risk of neuroblastoma (RR for G/A vs. A/A: 0.58; 95% CI: 0.38, 0.87 and RR G/G vs. A/A: 0.51; 95% CI: 0.26, 1.03). The maternal rs729147 was also significant for "total exposure" with very similar point estimates, but wider confidence intervals due to low numbers of variant alleles in "low vitamin A intake" (Figure 12).

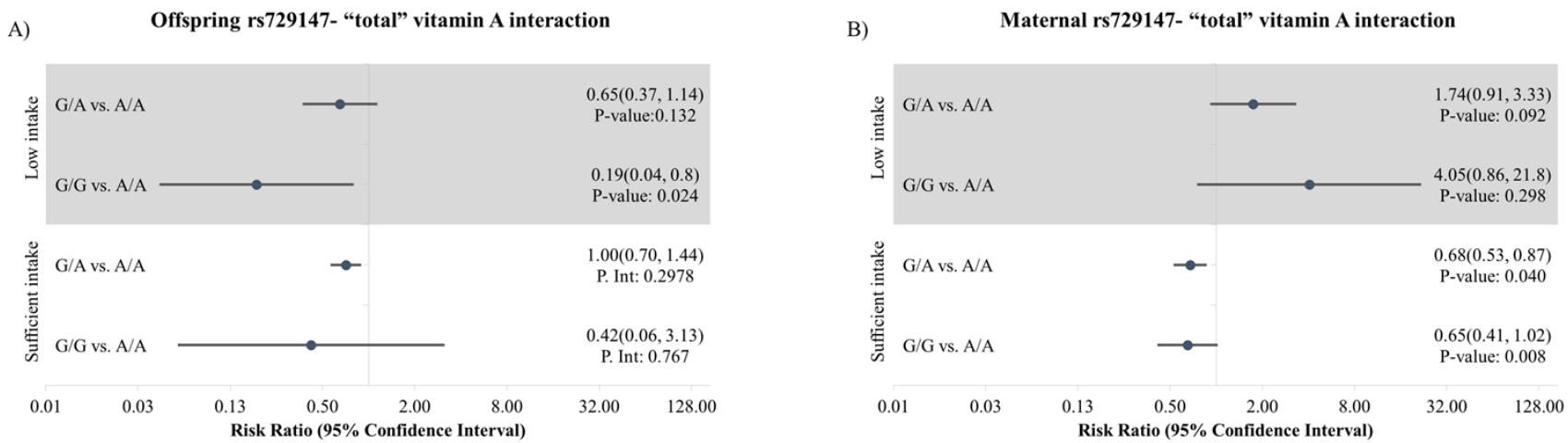
Figure 11. A) Offspring and B) Maternal interaction with co-dominant rs729147 with vitamin A dichotomized at the RDA (700 µg RAE)





Int.P: Interaction p-value

Figure 12. A) Offspring and B) Maternal interaction with co-dominant rs729147 "total" maternal vitamin A exposure



Int. P.: Interaction p-value

3.4.1 Replication Study

Maternal genotyping and questionnaire data were not available from CHOP, thus only offspring genetic results were compared. Similar to NENA's results, none of the offspring SNPs from CHOP were significant (Appendix 1), but unlike NENA, results based on CHOP were non-significant with stratification by risk-classification and offspring age at diagnosis (Results not shown). Additionally, the significant NENA results for intermediate-risk neuroblastoma, 3 of which were available in CHOP, did not replicate (Table 2).

3.4.2 Sensitivity Analysis

Among women below the RDA for vitamin A (700 μg RAE), 29 women reported that they had greatly increased their dairy intake during pregnancy compared to current diet. When these women were re-classified and the model refit, the maternal rs729147 was still significant. After breastfeeding mothers were excluded (N=47), no SNPs were significant, but the point estimate for the effect of rs729147 was in the same direction

3.5 Discussion

Vitamin A is crucial for proper differentiation of neuronal cells, and given the previous epidemiologic association with maternal vitamin supplementation pre-pregnancy, we hypothesized that common variants in the vitamin A pathway is associated with neuroblastoma and may be modified by maternal vitamin intake. Overall, no offspring SNPs were associated with neuroblastoma. Although some SNPs were associated with intermediate-risk neuroblastoma, these 3 SNPs did not replicate in the CHOP case-control validation study. Results from this study suggest that maternal variants may play a larger in neuroblastoma development (including different neuroblastoma subtypes) than offspring genetics. Moreover, maternal genetic effects may be modified by maternal vitamin A intake. However, since

maternal genotypes were not collected in the CHOP validation, the robustness of these findings is uncertain.

The A allele of maternal rs12442054 (minor allele frequency in mother = 6.1% and minor allele frequency in father = 13.7%), was associated with decreased risk of neuroblastoma. Although selected for its proximity to *STRA6*, this SNP is closest to the start site of *ISLR*. The exact function of *ISLR* in humans has yet to be determined, but in mice it is expressed the heart, thyroid, spinal cord and retina.[337] We were more inclusive when selecting variants, extending far beyond cis-regulatory elements, allowing us to capture some of the trans-regulatory elements. Research has shown that these intergenic regions can code for trans-regulatory elements such as intergenic binding sites for transcription factors or non-coding RNA – RNA not translated to proteins such as transfer RNA or ribosomal RNA.[338] There is evidence that rs12442054 is located within non-coding RNA, but the function of the non-coding RNA is unknown.[32]

We found 9 offspring SNPs significantly associated with intermediate-risk neuroblastoma. The functionality of these variants are unknown and they have not previously been associated with any disease. We found no SNPs of interest highly correlated ($r^2>0.8$) with these SNPs in 1000 Genomes CEU population using the SNAP software developed by the Broad Institute.[339] The intermediate-risk neuroblastoma group, as defined for prognostic use, is genetically very heterogeneous and the etiologic significance of our finding is unclear. Three of these significant SNPs were available in the CHOP validation case-control study and were not even directionally consistent with the NENA results, further highlighting the heterogeneity of intermediate-risk neuroblastoma phenotype and the uncertainty of the interpretation of these findings.

Two maternal SNPs were associated with neuroblastoma in our stratified analysis. We found that mothers with the T allele of the intronic rs6776706 in *RARB* had decreased risk of an offspring with high-risk neuroblastoma. No association was seen for this SNP with either low-risk or intermediate-risk neuroblastoma. Genome-wide association studies have found distinct variants associated with high-risk neuroblastoma, suggesting this prognostic category may have etiologic relevance.[44,79,81,83] One SNP, rs6800566, is in linkage disequilibrium with rs6776706 (r^2=0.96) and has been previously associated with measles virus antibodies and IL-10, IFN-α and TNF-α secretion in 745 Caucasian subjects.[340] However, the relevance of this SNP to neuroblastoma is unknown.

The T allele of maternal rs11103603, almost 10kbp downstream from *RXRA,* was associated with decreased risk of neuroblastoma in infants. This maternal variant was not associated with neuroblastoma in children older than 1 year (RR: 1.07; 95% CI: 0.84, 1.37). It is located in a CTCF binding site, which is a transcription regulatory site in embryonic human stem cell cultures; but how this SNP affects the binding site in unknown.[341,342] A variant in rs9409929 that is in high linkage disequilibrium with rs11103603 (r^2= 0.898), has been previously reported to be associated with increased levels of calcitriol – a hormonally active vitamin D metabolite.[343] Because vitamin D has been previously associated with decreased cancer risk,[344] this warrants additional study of the region in relation to vitamin D levels and neuroblastoma in infants. Unfortunately, since NENA did not collect blood samples, we are unable to directly address hypotheses related to vitamin D with the present study.

We found one significant result for a maternal gene-vitamin A interaction when vitamin A was dichotomized at the RDA value. This variant (rs729147) is 500bp downstream from *ADH7,* which encodes a gene that converts retinol to retinoic acid. *ADH7* is involved with

alcohol metabolism and rs729147 has been previously studied but no association with alcoholism was found.[345,346] SNPs in LD with this SNP have not been previously associated with any diseases. This SNP has never been studied in relation to vitamin A processing and transport and merits additional investigation.

This present study has a few limitations. Since the neural crest starts responding to differentiation signals at 5 weeks, our exposure window of interest is early pregnancy and pre-pregnancy.[71] However, we are using post-pregnancy usual diet as a proxy for this period and thus our dietary intake data is subject to measurement error. A few studies have demonstrated that maternal diet tends not to shift drastically during pregnancy,[306,307] but it is possible that current diet does not reflect early pregnancy diet, but rather pre-pregnancy diet before morning sickness if that occurred in the women. We also conducted a sensitivity analysis altering vitamin A due to dairy changes during pregnancy and confirmed that the association was not measurably affected by diet changes due to pregnancy. Additionally, our mothers were potentially interviewed during a time when their child was suffering from a critical illness, which could have substantially disrupted their routine behavioral patterns or influenced their reporting. However, we found little change in vitamin A consumption by risk-classification, a measure of severity of neuroblastoma.

Although we believe we had excellent coverage for the genes with SNPs selected from the CEU population, small proportion of the participants (93 mothers) are non-white, which may had less than ideal coverage. The violation of the assumption that the alleles of the mothers can be validly compared with the fathers can occur if there is uneven pairing by race leading to spurious maternal associations. However, when the non-white families were excluded, the point estimates were stable, suggesting that there is no violation of this assumption in NENA.

This study also had multiple strengths. Importantly, vitamin A has strong biologic plausibility with the etiology of neuroblastoma. Vitamin A is essential to the differentiation of neuronal cells. In neuroblastoma, less differentiated tumors present in a more aggressive fashion. Thus, 13-cis-retinoic acid is commonly used as maintenance treatment in conjunction with antibody therapy for high-risk neuroblastoma.[170] Vitamin A, in the form of retinol and retinyl ester or beta-carotene, is transferred from the mother to the placenta, highlighting the role of maternal genetics in fetal development and subsequent neuroblastoma malignant transformation.[139] Our use of the case-parent triad approach allowed for the assessment of these maternal genetic effects.

Additionally, this is the largest study to date with both genetic and maternal questionnaire data to allow for the study of gene-environment interaction. The case-parent triad approach eliminates the need for a control group. The Children's Oncology Group is the primary resource to collect a large number of cases. However, to collect population-based controls for a North-America-wide study would have presented a logistical and validity challenge. Additionally, the case-parent triad design is robust against bias due to population stratification and bias due to self-selection based on ethnicity. We also had access to the CHOP case-control study recruited from the same base population as NENA to independently validate the results from NENA.

In conclusion, we targeted variants in genes from the vitamin A pathway and found evidence that some genetic variants in vitamin A metabolism and transport may play a role in neuroblastoma etiology. However, due to the uncertain functionality of these SNPs, and the fact that some associations were seen only for sub-phenotypes, additional studies and replications of these results are warranted. .

CHAPTER 4: AIM 2 RESULTS

A family-based study of gene variants and maternal folate and choline in neuroblastoma: A Report from the Children's Oncology Group

4.1 Overview

Neuroblastoma is a childhood cancer of the sympathetic nervous system with embryonic origins. Previous epidemiologic studies suggest maternal vitamin supplementation during pregnancy reduces the risk of neuroblastoma. We hypothesized offspring and maternal genetic variants in folate-related and choline-related genes are associated with neuroblastoma and modify the effects of maternal intake of folate, choline and folic acid. The Neuroblastoma Epidemiology in North America (NENA) study recruited 563 affected children and their parents through the Children's Oncology Group's Children Cancer Research Network. We used questionnaires to ascertain pre-pregnancy supplementation and estimate usual maternal dietary intake of folate, choline and folic acid. We genotyped 955 genetic variants related to folate or choline using DNA extracted from buccal cell samples and used a log-linear model to estimate both child and maternal risk ratios and stratum-specific risk ratios for gene-environment interactions. Overall, no maternal or offspring genotypic results met criteria for a false discovery rate (FDR) Q-value <0.2. Associations were also null for gene-environment interaction with pre-pregnancy vitamin supplementation, dietary folic acid and folate. FDR significant gene-choline interactions were found for offspring SNPs rs10489810 and rs9966612 located in *MTHFD1L* and *TYMS*, respectively, with maternal choline dietary intake dichotomized at the first quartile.

These results suggest that variants related to one-carbon metabolism are not strongly associated with neuroblastoma. Some choline-related variants may play a role, however the functional consequences of the interacting variants of interest are unknown and require independent replication.

4.2 Background

Neuroblastoma is an embryonal tumor of the neural crest portion of the sympathetic nervous system and usually presents in children less than 1 year of age.[1,2] Each year approximately 770 children in North America are diagnosed with neuroblastoma, in which incidence rates slightly higher in males than females (7.7 per million vs 6.9 per million).[2,46,47,327] Familial cases of neuroblastoma have been associated with specific mutations in the *PHOX2B* and *ALK* genes and among non-familial cases, recent genome-wide association (GWA) studies have identified several common variants of interest.[6-9]

Due to the embryonic origins of neuroblastoma, pre-pregnancy and early pregnancy exposures are crucial its development. Epidemiologic studies have found evidence of an inverse association between maternal prenatal vitamin use and risk of neuroblastoma.[10,11] One study reported a 60% reduction in risk for daily vitamin use in the month before, or during pregnancy.

Although these studies did not indicate which vitamins(s) may underlie the association with neuroblastoma, folate and choline may be important. Folate is essential for one-carbon metabolism and is important in cell proliferation and differentiation of neural crest cells.[16,17] Choline is also involved in one-carbon metabolism and an essential building block for membrane development.[18]

Due to the key role of folate and choline in fetal and neuronal development and the suggestive epidemiological evidence, we hypothesized that genetically-based alterations in the levels of folate and choline during development, acting jointly with maternal nutrition, may impact the risk of neuroblastoma. This study is the first to examine the risk of neuroblastoma with maternal and offspring single nucleotide polymorphisms (SNPs) as well as gene-environment interactions with maternal folate and choline dietary intake and pre-pregnancy maternal vitamin supplementation.

4.3 Methods

4.3.1 Study Sample

The Neuroblastoma Epidemiology in North America (NENA) study used a case-parent triad design. Cases were identified from the Childhood Cancer Research Network (CCRN) – a registry system of newly diagnosed cases maintained by the Children's Oncology Group (COG).[304] NENA approached families registered in the CCRN registry who had agreed to be contacted for future research. Eligible cases had a primary diagnosis of neuroblastoma, including ganglioneuroblastoma but excluding ganglioneuroma. Cases had to be diagnosed before 6 years of age at a U.S. or Canadian COG institution from December 24, 2007 to July 31, 2013, and the biologic mother had to be alive and willing to participate. The University of North Carolina at Chapel Hill (UNC) Institutional Review Board approved this study.

After the cases were identified through the CCRN, we sent a recruitment packet to 1347 families and 870 families agreed to enroll. Study materials sent included a consent form, questionnaire to be filled out by the mother, a mouthwash Oragene saliva spit tube collection kit for the parents, and an Oragene saliva sponge/disc kit for the child. If the child was deceased, we delayed communication by 15 months after date of death and obtained a previously collected

blood DNA sample from the COG Neuroblastoma Bio-repository at the Children's Hospital of Philadelphia (CHOP).

Saliva samples were collected for 626 biological mothers, 592 living children, 525 biological fathers and blood samples were obtained for 19 deceased children (Figure 9). Of the 630 maternal questionnaires received, two did not have a corresponding signed consent form and two were incomplete, resulting in 626 completed questionnaires for analysis (Figure 10). Of the 630 maternal questionnaires received, two did not have a corresponding signed consent form and two were incomplete, resulting in 626 completed questionnaires for analysis.

4.3.2 Candidate Genes and SNP selection

Genes were selected based on their role in the transport and metabolism of folate and choline as well as one-carbon metabolism. Since most of the mothers self-identified as white, TAGster with the greedy algorithm was used to capture haplotype tagging SNPs (minor allele frequency ≥ 5%) that tag SNPs in high linkage disequilibrium (LD; $r^2 \geq 0.8$) for Hapmap 3 release III CEU population, located between 20kb upstream to 10kb downstream from the gene.[312,329] The case-parent triad design is not subject to confounding by population stratification, thus ancestry-informative markers were not included.[317] A total of 693 SNPs in 38 folate-related and 302 SNPs in 19 choline-related genes were selected for genotyping.

4.3.3 DNA collection and Genotyping

DNA extraction and amplification was completed by the UNC Biospecimen Processing Facility. DNA was extracted using the Perkin-Elmer's Chemagic MSMI magnetic-bead extraction robotic system. Saliva samples from parents were collected in DNA Genotek's OGR-250 collection kits. Saliva from the child was also collected by the parents using 5 provided

swabs to collect the saliva. The DNA quality was assessed with Nanodrop Optical Density and quantitated with Applied Biosystems® Taqman® RNase P detection kit. A total of 498 triads, 99 mother-child dyads, 5 father-child dyads and 27 other (mother-father dyads and singleton cases) with DNA yields greater than 2 µg were sent for genotyping.

Genotyping was performed by UNC's Mammalian Genotyping Core Facility using the GoldenGate Assay with the Illumina BeadStation 500GX Genetic Analysis System. Allelic discrimination was based on allele-specific primer extension followed by ligation.

4.3.4 Genotyping Quality Control

For quality control purposes, a Centre de l'Étude du Polymorphisme Humain (CEPH) family triad and blinded duplicates were included on each plate. SNPs with a genotyping call rate less than 95% and showing a lack of defined clusters in the raw genetic intensity data were excluded. Individual genotypes for SNPs showing apparent Mendelian errors in a particular family were treated as missing. In total, 599 folate-related SNPs and 277 choline-related SNPs passed quality control. We assessed Hardy-Weinberg (HWE) equilibrium among parents who self-identified as white using chi-square tests in PLINK (v1.07) and flagged (n=5), but did not exclude, SNPs that failed HWE at a false discovery rate (FDR) significance level of < 0.2.[330,331]

Individuals with genotyping rates <95% or gender discrepancies were excluded. Relatedness was confirmed for each triad through measures of identity by descent. Triads and individuals with unexpected relatedness were excluded. For example, for non-paternity the paternal data was excluded. A total of 465 triads, 94 mother-child dyads, 4 father-child dyads and 61 others (13 mother-father dyads and 48 singletons) passed genetic quality control (Figure 10).

4.3.5 Biological and Clinical Variables

We obtained clinical and biologic characteristics of the tumor, such as tumor genetics and stage, from the COG Statistical and Data Center for all cases enrolled in a COG clinical protocol except 89 cases who were not enrolled. The data also included the COG "risk-classification" variable using a schema that defined three prognostic risk-classifications: low-risk, intermediate-risk and high-risk. These risk-classifications are based on tumor characteristics, including stage and *MYCN* amplification, ploidy and patient age dichotomized at 1 year.[43]

4.3.6 Maternal Vitamin Use

We ascertained the current and usual maternal diet during the preceding year using the Dietary History Questionnaire, a self-administered semi-quantified food frequency questionnaire (FFQ). We assumed maternal usual diet in the last year approximates pre-pregnancy diet. Completed FFQs were processed in Diet*Calc (version 1.5.0) to derive usual nutrient intake per day for the previous year. The nutrient and food group database was based on a compilation of national 24-hour dietary recall data from the National Health and Nutrition Examination Surveys (NHANES) conducted in 2001-2002, 2003-2004, and 2005-2006 (http://riskfactor.cancer.gov/dhq2/database). Certain foods not included in the original database were added by NENA staff in 100 gram amounts using the USDA database, standard release 24.

To address potential differences between "usual" diet and diet during pregnancy, the questionnaire also asked if women had changed their consumption of foods prone to change, including dairy and fish.[309] The mothers were asked if during pregnancy intake of these foods was "Much less than it is now", "Somewhat less than it is now", "Same as it is now", "Somewhat more than it is now", and "Much more than it is now".

Mothers were also questioned about maternal dietary supplementation, including single vitamins and prenatal or multi-vitamin use 1 month pre-pregnancy and within each trimester of pregnancy. To aid in recall, an estimated conception date was provided; calculated by subtracting gestational age at delivery from infant birthdate. Since we are interested in pre-pregnancy and early pregnancy exposures, we focused on prenatal vitamin or multivitamin use 1 month pre-pregnancy.

4.3.7 Diet and Nutrient classification

We excluded questionnaires that reported calories per day below the 5th percentile (N=31; <854.47 calories) or above the 97th percentile (N=18; >4508.75 calories) (Figure 10). We focused on folate, folic acid and choline for gene-environment interaction. To take into account the different bioavailability of food folate and folic acid, dietary folate equivalent (DFE) was used to estimate total folate. To explore different dietary cutoffs, nutrients from the FFQ were dichotomized at the 25th percentile (<209.70 mg for choline; <389.83 μg DFE; and <100.69 μg folic acid) and current daily recommendation for adult women. For total folate, the recommended dietary allowance (RDA) is 600 μg DFE for pregnant women.[27] Given choline and folic acid does not have an RDA we used the choline Adequate Intake – a recommendation level when RDA is not available – for women (425 mg/day) and for folic acid we used the Public Health Service Task Force recommendation for women trying to get pregnant (400μg/day).[320,347]

We conducted an analysis combining prenatal or multi-vitamin use and folic acid and folate from diet. Maternal total exposure was split into two groups: low intake and sufficient intake. Women with intake in the lowest tertile of micronutrients from diet and with no prenatal or multivitamin supplementation 1 month pre-pregnancy were defined as “low intake”. A woman was classified as “sufficient intake” if she had greater than the 33rd percentile of micronutrients

from diet and/or took a prenatal or multivitamin supplement 1 month pre-pregnancy. We only combined vitamin use with folic acid and folate from diet, because choline is not commonly found in prenatal vitamins.

4.3.8 Statistical Analysis

There were three main analytic goals: 1) estimate the genotypic maternal and offspring risk ratios (RRs); 2) estimate stratum-specific RRs by neuroblastoma prognostic risk-classification and offspring age at diagnosis; and 3) assess multiplicative maternal and offspring gene-environment interactions with maternal choline, folate and folic acid intake. We used a log-linear model to simultaneously assess the offspring and maternal log-additive genetic main effects and gene-environment interaction.[317]

Since there are no study controls in this analysis, the null background is discerned from the parental genotypes under the assumption of Mendelian transmission in the source population.[317] For assessing a maternally-mediated genetic association, the maternal genotype frequencies are compared to the paternal genotype frequencies under a further assumption of mating symmetry in the source population. The maternal and offspring log-additive RRs were calculated simultaneously and thus are mutually adjusted. Missing parent genotypes can be accounted for with the expectation-maximization algorithm, which maximizes the observed-data likelihood by fractionally assigning incomplete triads into their data-compatible cells on the basis of the current parameter estimates, and then repeating the calculations iteratively up to convergence and maximization of the likelihood.[20]

For the stratified analysis, the offspring and maternal genetic models were separately fit for each prognostic COG risk-classification and offspring age at diagnosis dichotomized at 1

year with separate "mating type" and risk parameters allowed within each stratum. "Infant cases" are less than 1 year of age at diagnosis, while "childhood cases" are those greater than or equal to 1 year of age. This age dichotomy represents the two peaks in the neuroblastoma age at diagnosis distribution.

The gene-environment interaction model is an extension of the genetic only model with an additional term for the interaction of the offspring or maternal genotype and maternal vitamin intake.[21] This model allows genotypic RRs to differ across levels of vitamin intake. The main genotype effects were coded co-dominantly, while the interaction term is fit additively to enhance power. If interaction terms were significant after multiple testing correction, then the interaction model was refit co-dominantly to characterize the interaction in a more flexible way.

All p-values were corrected for the number of tests by false discovery rate (FDR).[334] Results were considered significant if the FDR-corrected Q-value was less than 0.2. All estimated RRs are presented in relation to the minor allele at the specified SNP.

4.3.9 Replication Study

We were able to provide replication of our findings for offspring genotypes using genotyping data from a previously conducted GWA study. Dr. John Maris and colleagues at CHOP conducted a GWA case-control study with 2,101 neuroblastoma cases and 4,202 healthy controls of European-American ancestry. Information on this study has been described elsewhere.[8] Briefly, the cases were diagnosed with neuroblastoma and identified through the Neuroblastoma Bio-repository maintained by the COG, which collects germline and tumor specimens at the time of diagnosis. Controls with no known medical disorder were recruited from multiple sites within the CHOP Health Care Network, including four primary care clinics

and several group practices and outpatient practices. Principle component scores were used to adjust for population stratification. Cases that were enrolled in NENA were excluded from the CHOP sample, resulting in 2,052 cases and 4,104 controls.

Imputation was performed on all CHOP case-control GWA data with IMPUTE2 using the world-wide 1000 Genomes Project Phase 1 interim data as reference (June 2011 release).[335] Additional information about the imputation has been previously published.[8] The same SNPs used for the NENA case-parent analysis (N=1173) were tested for case-control association with neuroblastoma using SNPTEST under the additive model.[335] About a third of these SNPs were imputed in the CHOP replication study. Odds ratios (ORs) were FDR-corrected and compared with the RRs from NENA.

4.3.10 Sensitivity Analysis

Since many women increase dairy consumption and decrease fish consumption during pregnancy, and both are large contributors to choline, we performed sensitivity analyses. The questionnaire asked if women changed their diet relative to current diet in foods prone to change, including dairy and fish.[309] The mothers were asked if during pregnancy intake was "Much less than it is now", "Somewhat less than it is now", "Same as it is now", "Somewhat more than it is now", and "Much more than it is now".

Choline levels were manually changed for women to reported increasing dairy consumption and decreasing fish consumption during pregnancy. We calculated the average amount fish and dairy contributes to choline in NENA. Choline levels for mothers who reported that their fish consumption during the pregnancy had been "much less than it is now" were decreased by 8.55 mg. For mothers who reported that their dairy consumption during the

pregnancy had been “much more than it is now”, their choline levels were increased by 73.87 mg, the average amount of choline. After this choline intake adjustment, choline was then dichotomized at the 25th percentile and the gene-environment model was fit again.

Since women who breastfeed are advised to consume more calories, which alters current nutrient intake, additional sensitivity analyses were done excluding breastfeeding women.

4.4 Results

4.4.1 Descriptive Statistics

We had genetic data for 465 triads and 98 dyads. Descriptive statistics for triads with genetic data are shown in Table 13. The mean age at diagnosis for the offspring was 1.7 years. As expected, the age at diagnosis differed across COG risk-classifications (p-value < 0.001) and the high-risk classification had the oldest age at diagnosis (2.6 years). Maternal age at birth was consistent across risk groups with the overall average maternal age of 29.8 years. There were more male (53.6%) than female cases in the study. This pattern of male excess was consistent across COG risk-classification groups except for the low-risk group (52.4% females). The predominant maternal race was white (84.8%). The median vitamin A maternal consumption was 672.21 μg RAE (Interquartile range: 458.18-978.16).

Table 13 describes the demographics of our analytic sample of families (465 triads and 98 dyads). The mean age at diagnosis for the offspring was 1.7 years. As expected, the age at diagnosis differed across COG risk-classifications (p-value<0.001); the high-risk classification had the oldest mean age at diagnosis (2.6 years). Maternal age at birth of the case was similar across risk-classification categories. This study included more male cases (53.6%) than female cases. This male excess was similar across COG risk-classification groups except for the low-risk classification (52.4% females). The predominant maternal race was white (84.8%). Almost

60% of mothers (N=349) reported using vitamin supplementation 1 month before conception. (Table 16).

Table 16. Descriptive statistics of maternal usual dietary nutrient levels and supplemental pre-pregnancy vitamin consumption

	N	%
Vitamin use 1 month pre-pregnancy		
Yes	349	59.4
No	239	40.6
Missing	36	--
	N	Median (IQR)
Choline (mg)	559	279.78 (208.28-372.39)
Folate (Dietary Folate Equivalent)	559	511.29 (389.71 - 698.35)
Folic Acid (µg)	559	162.11 (100.69-233.79)

4.4.2 Folate

We found no significant associations between folate-related maternal and offspring SNPs and neuroblastoma overall, or when stratified by COG risk-classification or offspring age at diagnosis (**Appendix 3 and 4**).

We observed no significant gene-environment interaction in relation to maternal or offspring genotypes for maternal vitamin supplementation 1 month pre-pregnancy or for maternal dietary folic acid or total folate intake. Results from the total exposure analysis combining prenatal and multi-vitamins and diet were also non-significant.

4.4.3 Choline

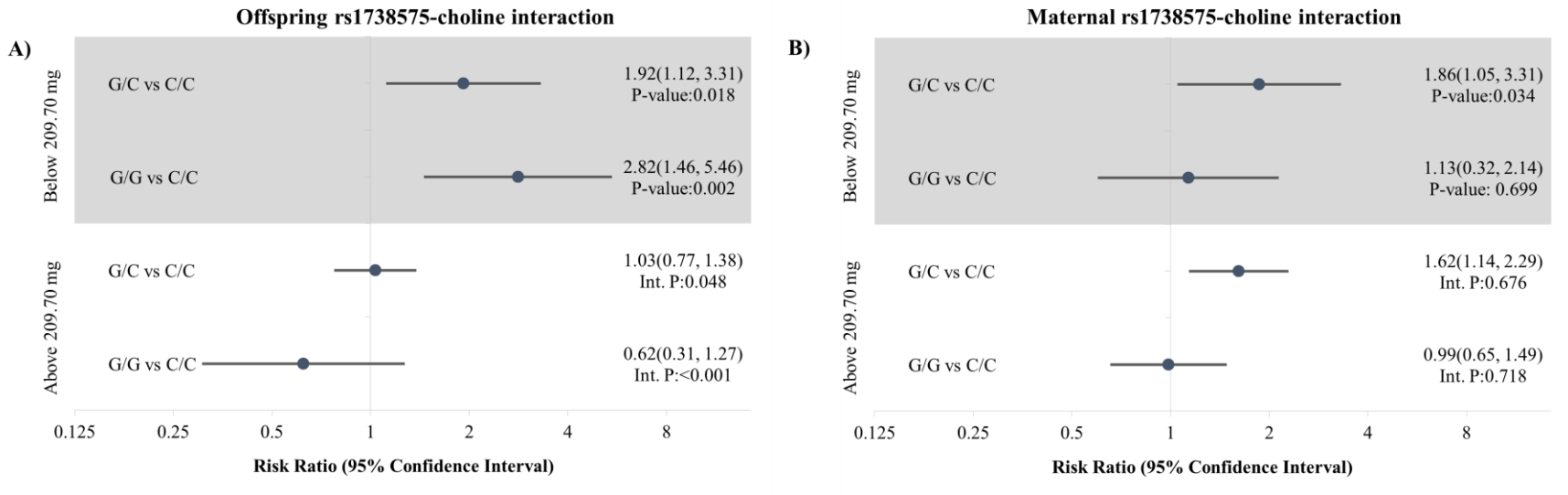
We found no significant associations for maternal or offspring choline SNPs, either overall or stratified by risk-classification or offspring age at diagnosis.

For the gene-choline interaction, we observed two significant log-additive interaction p-values for the 25th percentile in maternal choline consumption with the offspring SNP rs1738575 (interaction p-value<0.001; Q-value=0.076), and with the offspring SNP rs9966612 (p-

value<0.001; Q-value=0.140). We refit the interaction model co-dominantly to provide allele-count-specific point estimates resulting in wider confidence intervals due to the rarity of homozygotes. For mothers below the 25th percentile of choline consumption (Figure 13), when maternal choline consumption was below the 25th percentile (RR for A/G versus G/G: 0.46, 95% CI: 0.30-0.70; RR for A/A versus G/G: 0.5, 95% CI: 0.21-1.21), with both lower than the relative risks among triads with maternal choline greater than the 25th percentile (RR for A/G versus G/G: 1.35, 95% CI: 1.04-1.75; RR for A/A versus G/G: 1.08, 95% CI: 0.31-3.75).

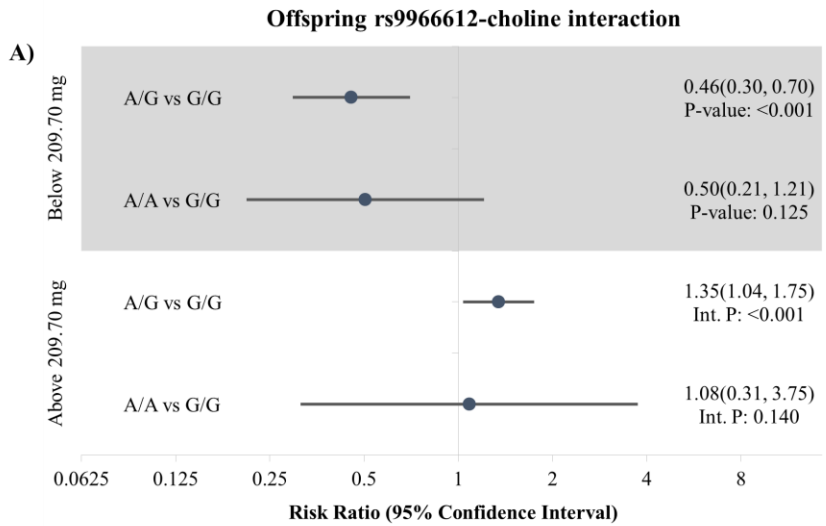
When choline was dichotomized at the Adequate Intake level (425 mg), the log-additive interaction was significant for the offspring SNP rs10489810 (interaction p-value<0.001; Q-value=0.173). Among mothers with below Adequate Intake of choline consumption, we found offspring with one T allele had little evidence for association (RR T/A vs. A/A: 0.91, 95% CI: 0.71-1.17) while those with 2 T alleles had an inverse association (RR T/T vs. A/A: 0.43, 95% CI: 0.26-0.70). Among mothers with above Adequate Intake level of choline, offspring with 1 T allele and those with 2 T alleles had an increased risk (RR T/A vs. A/A: 2.00, 95% CI: 1.11-3.60; RR T/T vs. A/A: 2.85, 95% CI: 0.98-8.30) of neuroblastoma.

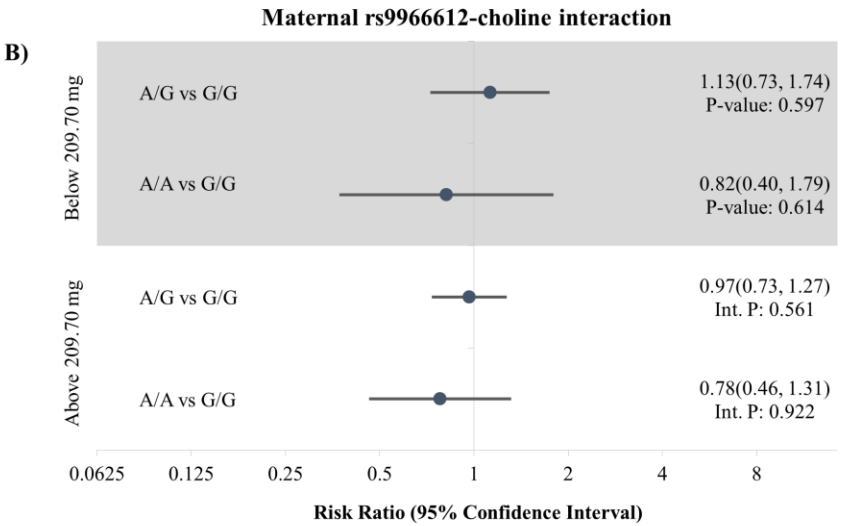
Figure 13. A) Offspring and B) maternal interaction with codominant rs173857 and maternal choline dichotomized at the 25th percentile



Int.P: Interaction p-value

Figure 14. A) Offspring and B) maternal interaction with codominant rs9966612 and maternal choline dichotomized at the 25th percentile





Int. P.: Interaction p-value

4.4.5 Replication Study

Maternal genotyping and questionnaire data were not available from CHOP, thus only offspring genetic results were compared. There are a few CHOP study results that are significant (**Appendix 3**). However, the results from NENA for these SNPs were not also significant and the RRs were not directionally consistent between studies.

4.4.6 Sensitivity Analysis

Among women who were below the 25th percentile for choline, 10 mothers increased dairy consumption and 2 increased fish consumption during pregnancy. For women with greater than the 25th percentile for choline consumption, 8 decreased dairy consumption, but 83 decreased fish consumption during pregnancy. In the sensitivity analyses, both alleles for rs10489810 and rs9966612 remained significant (Table 17) and the point estimates changed little. We also found a significant interaction with offspring alleles in rs9478157 and rs1052751, neither of which had previously been significant.

We found no new significant results when women who were breastfeeding were excluded (N=46). The previously identified gene-choline interactions for offspring SNPs rs10489810 and rs9966612 remained nominally significant and were directionally unchanged.

Table 17. Choline sensitivity analysis with offspring SNPs

		Below 209.70 mg Choline Consumption						Above 209.70 mg Choline Consumption			
SNP	Gene	RR - (95% CI) 1 Allele	P	Q	RR (95% CI) 2 Alleles	P	Q	RR(95% CI) 1 Allele	RR (95% CI) 2 Alleles	Int. P	Int. Q
rs1052751	*PLD2*	2.63(1.42,4.86)	0.002	0.398	6.49(2.05,20.6)	0.002	0.534	0.88(0.66,1.17)	0.72(0.34,1.52)	0.001	0.133
rs1738575	*MTHFD1L*	2.06(1.35,3.16)	0.001	0.398	2.60(1.27,5.33)	0.009	0.825	0.99(0.76,1.31)	0.60(0.40,0.91)	0.001	0.133
rs9478157	*MTHFD1L*	1.87(1.22,2.87)	0.004	0.508	2.89(1.3,6.44)	0.009	0.825	0.86(0.67,1.1)	0.61(0.39,0.95)	0.001	0.133
rs9966612	*TYMS*	0.53(0.35,0.8)	0.003	0.398	0.21(0.09,0.52)	0.001	0.520	1.25(0.97,1.63)	1.20(0.72,1.99)	0.000	0.133

RR: Risk Ratio; **CI**: Confidence Interval; **P**: P-value; **Q**: FDR Q-Value; **Int. P:** Interaction P-value; **Int. Q:** Interaction FDR Q-value

4.5 Discussion

These analyses were motivated by prior epidemiologic evidence suggesting that inadequate maternal consumption of folate, folic acid, and choline is increases the risk of neuroblastoma. Although SNPs within the one-carbon metabolism pathway have been previously associated with birth defects and childhood cancers, our study suggests these SNPs may not play a direct role in the etiology of neuroblastoma.[178,232,252,348] SNPs from either choline or folate-related genes were not associated with neuroblastoma overall, within COG risk-classification, or by age at diagnosis. While significant SNPs were found in the CHOP case-control replication study, those SNPs were not significant and were not directionally consistent with NENA results. The gene-environment interaction results suggest gene variants in choline pathways may modify effects of choline intake; however, since the identified SNPs lie within non-coding regions, the exact implications of these associations are unclear at present.

We found no offspring or maternal associations for the SNPs that were selected because they had previously been associated with cancer or birth defects. *MTHFR* 667C>T (rs1801133), one of the most highly studied variants with known functional effects on one-carbon metabolism,[228,233,235] had a non-significant offspring RR of 0.99 (95% CI: 0.84-1.19) and a weak maternal RR of 1.16 (95% CI: 0.97-1.38). Two previous studies of candidate SNPs from folate-related genes identified *SLC19A1* 80G>A (rs1051266) as positively associated with neuroblastoma in Brazil.[85,86] Montalvão-de-Azevedo et al. found maternal carriers of the G had 3 times the risk of offspring with neuroblastoma and offspring carriers had approximately 2.5 times the risk, which was replicated by de Miranda et al.[85,86] We found no association in NENA (Maternal RR: 1.12, 95%: CI: 0.96-1.32; offspring log-additive RR: 0.94, 95% CI: 0.79-1.11). The inconsistent findings may be due to chance, differences in ancestry, confounding by

maternal genotype, or possibly different dietary and vitamin supplementation intake patterns in Brazil.

We found significant gene-choline results for two offspring SNPs, rs1738575 and rs9966612, respectively located in an intron of *MTHFD1L* and upstream from *TYMS*. MTHFD1L is involved in tetrahydrofolate conversion in the mitochondria during one-carbon metabolism.[16] Offspring SNP rs9966612 is about 8 kbp upstream from *TYMS* but within the intron of *CLUL1* and 500 bp downstream from *TYMSOS.* However, there is no compelling evidence either *TYMSOS* or *CLUL1* is related to neuroblastoma development.[349] Since we used haplotype tagging, these SNPs could be in LD with the casual SNP. To further explore correlated SNPs, we used SNP Annotation and Proxy Search (SNAP) developed by the Broad Institute to find SNPs in high LD (r^2>0.8) based on the 1000 Genome CEU population.[339] SNPs in high LD with rs1738575 and rs9966612 have not previously been associated with disease. Given these SNPs are located in regions not previously identified as transcriptionally active, their impact is unclear.

When choline was dichotomized at the Adequate Intake level, we found one additional interacting offspring SNP, which appeared to increase the risk of neuroblastoma among those above the Adequate Intake level but decrease risk among offspring below. The offspring SNP rs10489810 is located within an intron of *SLC44A3*, a choline transporter. SNPs in *SLC44A3* and those in high LD with rs10489810 have not previously been associated with any disease.

This present study has some limitations. Our assessment of pre-pregnancy maternal diet is retrospective. Studies have demonstrated that maternal preconception nutritional status is critical for early fetal development but the critical etiologic window specific to neuroblastoma is nonetheless unknown; thus, our exposure window extends from pre-pregnancy until early

pregnancy.[350] The mothers in NENA completed the FFQ shortly after enrollment (2 months to 9 years after the offspring birth date). This assessment of diet more likely mirrors pre-pregnancy diet rather than early pregnancy when mothers may have changed diet due to morning sickness.[351] Moreover, the FFQ occurred during a time when their child was suffering with a critical illness or may have died, leading to the potential for substantial disruption of their routine eating patterns. However, in our data nutrient levels of folic acid, folate and choline from diet did not significantly differ by risk-classification or vital status, suggesting that nutrient levels do not differ by severity of disease. Furthermore, our sensitivity analysis revealed the FDR-significant SNPs for gene-choline interaction were stable to differences in the estimation of choline levels related to reported changes in fish and dairy consumption during pregnancy. The population studied in NENA were mostly white and highly educated (over 50% graduated college), and thus have greater rates of vitamin consumption and nutrient intake compared to the general population in the United States.[98] Although the nature of our study sample does not affect the validity of the study, it could reduce generalizability and introduces the possibility that we are not capturing the "high risk" population that could benefit the most from intervention.

The study has multiple strengths. This is the largest study conducted to date with both genetic and maternal questionnaire data to allow for the study of gene-environment interaction for genes in exposure pathways with evidence for an association with neuroblastoma. The case-parent triad approach eliminates the need for a control group, a logistical and validity challenge for a North America-wide study. Additionally, the case-parent triad design is robust against bias due to population stratification and self-selection based on ethnicity. The case-parent triad approach also allows for the estimation of maternal risk ratios, which is especially important for diseases that can originate in utero. We employed the use of an independent Replication study

that provided additional evidence for the robustness of our null results for offspring SNPs and neuroblastoma.

This study suggests that maternal and offspring SNPs in folate and choline-related genes are not strongly associated with neuroblastoma. Further, gene-environment interactions were not found for maternal vitamin supplementation or total folate or folic acid intake from diet, suggesting there is no appreciable modification of effects of SNPs near folate and choline-related genes by maternal diet or vitamin supplementation. We did find some suggestive associations for the choline pathway, which warrant further study.

CHAPTER 5: DISCUSSION AND CONCLUSIONS

5.1 Summary of Specific Aims

In epidemiologic studies, there have been suggestive associations between maternal vitamin supplementation during pregnancy and a decreased risk of neuroblastoma. This suggests that micronutrients in prenatal vitamins may be important to neuroblastoma development.[10,11] We decided to focus on vitamin A, folate and choline because of strong biologic plausibility. Vitamin A is involved in the differentiation of neuroblasts during fetal development and used in the preventative therapy of neuroblastoma recurrence after treatment.[12,13,170] Folate and choline both are involved with DNA maintenance through one-carbon metabolism.[16,18]

We assessed the importance of these vitamin pathways by investigating maternal and offspring single nucleotide polymorphisms (SNPs). In Aim 1, we estimated the association between haplotype tagging SNPs in or near genes involved in vitamin A metabolism and transport and neuroblastoma overall and stratified by Children's Oncology Group (COG) prognostic risk-classification or offspring age at diagnosis. Additionally, we assessed the interaction of these variants with maternal vitamin A consumption measured through diet and use of prenatal vitamin or multivitamin supplementation pre-pregnancy.

In Aim 2. We estimated the association between maternal and offspring SNPs from genes involved in the metabolism and transport of choline and folate on neuroblastoma overall and stratified by COG risk-classification and offspring age at diagnosis. We also assessed the

interaction of these maternal and offspring variants with maternal folate, choline and folic acid consumption measured through diet and use of vitamin supplementation pre-pregnancy.

We also performed an independent a replication case-control study of offspring SNPs using genome-wide association (GWA) data provided by Dr. Maris and colleagues at the Children's Hospital of Philadelphia (CHOP).

5.2 Summary of Results

5.2.1 Aim 1

We found rs12442054, selected for its proximity to *STRA6*, inversely associated with neuroblastoma at a false discovery rate (FDR) Q-value < 0.2. We found 9 offspring FDR-corrected SNPs significantly associated with intermediate-risk neuroblastoma in 4 genes (*RXRA*, *ADH1A*, *RARG*, and *ALDH1A2*). However, of the three SNPs also available in the CHOP replication case-control study, none were significantly associated with intermediate-risk neuroblastoma. In our stratification analysis, one maternal SNP was associated with high-risk neuroblastoma and another SNP was associated with infant neuroblastoma (age of diagnosis <1 year). We found mothers with the T allele of the intronic rs6776706 in *RARB* had a decreased risk of an offspring with high-risk neuroblastoma. The T allele of maternal rs11103603, located almost 10kbp downstream from *RXRA*, was associated with decreased risk of neuroblastoma in infants.

We found no FDR-corrected significant interaction with SNPs in or near vitamin A-related genes with maternal prenatal or multi-vitamin supplementation pre-pregnancy. A FDR-corrected significant gene-vitamin A interaction was observed when vitamin A intake was dichotomized at the Recommended Dietary Allowance (RDA). Among mothers with vitamin A intake below the RDA, the maternal SNP rs729147, located near *ADH7*, was associated with

increased risk of neuroblastoma. When maternal intake was above the RDA, the SNP was associated with a decreased risk of neuroblastoma.

To test gene-environment interaction with "total" nutrient exposure, we combined nutrients from vitamin use pre-pregnancy and diet by classifying women with above the 33rd percentile nutrients from diet or taking vitamin pre-pregnancy as sufficient nutrient intake and those without vitamin pre-pregnancy use and low nutrient intake as low nutrient intake. When we assessed gene-vitamin A interaction with "total" vitamin A exposure, rs729147 was also significant.

5.2.2 Aim 2

Overall, none of the selected offspring or maternal SNPs in or near folate and choline-related genes were FDR-corrected significant overall, or after stratification by COG risk-classification or offspring age at diagnosis. Moreover, most SNPs that had been previously reported to be associated with birth defects and childhood cancers (including neuroblastoma) were not significant, even at an uncorrected nominal alpha of 0.05.[86,227,352,353]

We found FDR-corrected significant gene-environment interactions for 3 SNPs with maternal choline, but none with folic acid, folate, pre-pregnancy vitamin supplementation or "total" exposure for folic acid and folate. Two offspring SNPs (rs1738575 and rs9966612) had a significant gene-choline interaction with maternal choline consumption dichotomized at the 25th percentile. Among mothers with choline intake in the 25th percentile, offspring with the G allele of rs1738575 had an increased risk of neuroblastoma. However, among mothers with intake greater than the 25th percentile, no association was found with offspring rs1738575. Among mothers with choline intake in the 25th percentile, offspring with the A allele of rs9966612 was inversely associated with neuroblastoma. However, among mothers with intake greater than the

25th percentile, the offspring A allele of rs9966612 had a positive association. When choline was dichotomized at the Adequate Intake (the recommended value in the absence of an established RDA) for choline, we found that the T allele of offspring rs10489810 increased the risk of neuroblastoma among those above the Adequate Intake, but decreased risk among offspring with maternal choline consumption below the Adequate Intake.

5.3 Strengths and Limitations

5.3.1 Strengths

This study is the largest epidemiologic study with both genetic and exposure data to date, allowing us to assess gene-environment interaction. Previous studies either only examined genetic associations[8,84] or only examined environmental exposures.[119,120,122,132,137] Previous genome-wide association (GWA) studies have identified offspring variants associated with non-familial neuroblastoma, indicating that there is a genetic component to neuroblastoma.[8,84]

We chose to focus on a candidate gene approach to explore gene regions with strong biologic plausibility and have greater power to study gene-environment interactions and stratification by COG risk-classifications. Due to the previous epidemiologic associations with prenatal vitamin use and biologic plausibility, we focused on three vitamins (vitamin A, folate and choline). Since vitamin A is essential for neuronal development and differentiation, *cis*-13 retinoic acid (a metabolite of vitamin A) is used a preventative therapy in children after treatment for high-risk neuroblastoma. Low levels of choline and folate from diet and genetic variation have been associated with a myriad of developmental disorders.[285,286,291] Previous candidate SNP studies that have assessed maternal and offspring folate-related SNPs have had small sample sizes (fewer than 100 cases) and concentrated on a few SNPs.[85,86]

This is the first study to examine gene-environment interaction after initiation of folic acid fortification in the United States and Canada. This makes the study more generalizable to the current population in the United States, in which folic acid and folate consumption in general increased in the United States.[354] This increase in folate consumption has shifted the distribution where more women have folate consumption above the RDA thus increasing the power to detect an association.[223]

Since neuroblastoma is embryonal in nature, the fetal developmental environment plays a large role in its development. The maternal ability to process and transport micronutrients is essential for proper fetal environment.[139,355] The case-parent triad design allows us to estimate maternal genetic risk ratios and assess maternal gene-environment interaction.[1] The case-parent triad approach is also robust against population stratification without having to genotype additional ancestry informative markers. This is particularly beneficial for this study. Since neuroblastoma is rare, to amass the proper number of cases, families were recruited from both Canada and the United States. Given the wide scope of the case ascertainment encompassing many different racial groups, to properly conduct a case-control study by recruiting a proper North American control group presented a logistical as well as a validity challenge. Additionally, case-parent triads allow the inclusion of families with missing paternal genotypes though the expectation maximization algorithm, which makes full use of the available data to boost power.[20]

5.3.2 Limitations

This study had a few limitations. We are interested in maternal nutrition status early pregnancy and pre-pregnancy because the neural crest migrates and begins to differentiate by 5 weeks into pregnancy.[71] We are assuming that current usual maternal diet is an adequate

approximation for diet during our exposure window of interest. Nonetheless, we assumed that the misclassification that could be introduced by a long recall period (average recall from questionnaire completion to conception: 3.1 years).[356] Moreover, studies conducted to assess changes in diet due to pregnancy determined that in general diet does not vary in relation to other individuals.[306-308] Our measurement of diet post-pregnancy should be representative of pre-pregnancy diet before morning sickness alters diet dramatically. The maternal current diet may be influenced by the offspring's neuroblastoma diagnosis. However, nutrient levels did not significantly vary across COG risk-classification – a proxy for the severity of disease – suggesting the diagnosis event did not alter levels diet drastically. The questionnaire also asked about diet for the last year to minimize the influence of the diagnosis and to capture usual diet.

To help address the possible differences between current usual diet and diet during pregnancy, the NENA questionnaire asked the mothers if during pregnancy intake of foods prone to change – such as dairy, citrus, juices, fruit, meat, coffee, diet soda and alcohol drinks – was "Much less than it is now", "Somewhat less than it is now", "Same as it is now", "Somewhat more than it is now", and "Much more than it is now".[309] Within NENA, fish was commonly reported decreasing during pregnancy and dairy was commonly reported increasing during pregnancy compared to the current usual diet. To assess the robustness of our FDR-corrected significant vitamin A and choline gene-environment interaction results, we altered vitamin A and choline levels for women increasing dairy or decreasing fish. After dichotomizing the new altered nutrient levels and refitting the gene-environment model, our point estimates were similar, suggesting that our significant results are stable to changes in diet.

Because many women (~50%) were not able to recall the brand of prenatal or multi-vitamin taken, we could not calculate the amount of a nutrient derived from supplementation and

accurately combine vitamins from diet and supplementation. However, we were able to calculate a "total" exposure by defining sufficient intake as women who either had above the 33rd percentile or had taken pre-pregnancy vitamin supplementation.

We are also underpowered to detect weak associations. We have power to detect risk ratios of 1.5 at an alpha of 0.001. Since we are underpowered, we only corrected for the number of SNPs studied by the nutrient-specific pathway rather than for all the SNPs studied and for each risk-stratification of neuroblastoma. This gives us more power, but also makes it more likely to have committed a type 1 error.

The case-parent triad approach also has a few assumptions that could be violated, such as Mendelian inheritance and parental symmetry.[19] Disruption of Mendelian inheritance could occur if embryos that are homozygotes for a variant allele do not survive, in which such attrition would lead to results where two alleles appear to confer lower risk than one allele. However, if this were the case, such an allele would be quickly selected out of the population. Spurious significant maternal associations can arise if the mating symmetry is violated (i.e. a genotype is over represented in either the mother or father not due to the disease state of the offspring). The most likely scenario for violation is racial differences between the parents. When we restricted the analysis to only white mother-father pairings, the maternal results remained significant and unchanged, implying that this assumption is not likely violated. Another crucial assumption is that missingness is non-informative. The most likely source of this violation would be if paternal genotype and participation both depend on paternal race, conditional on the observed mother-child genotype. This is unlikely to have a major influence, given the small number of non-white mothers and fathers in NENA.

We are also unable to study any trimester specific gene-environment interactions with maternal vitamin supplementation because of high number of mothers taking prenatal or multi-vitamins. Most of the mothers enrolled in NENA reported taking a multivitamin or prenatal vitamin 1 month pre-pregnancy (60%) and by the 1st trimester over 90% of the mothers had started taking vitamins. This prevalence of vitamin use was much higher than reported for another neuroblastoma case series pre-fortification in the United States and previous reports of vitamin supplementation among pregnant women.[10,97] The majority of NENA mothers were white and highly educated (over 50% have at least some college education), a sub-group that has been previously shown to have higher levels of vitamin supplementation during pregnancy.[97,357] Moreover, during the time period of previous neuroblastoma case series (1992–1995), knowledge of the prenatal vitamin supplementation was low. Public Health Service did not recommend folic acid supplementation until 1992. In a March of Dimes telephone survey in 1995, only 52% of women have heard of folic acid and only 28% took a supplement.[358] Women who enrolled in our study were more likely to have health seeking behavior, possibly explaining our higher prevalence of vitamin supplementation. Since this study is not dependent on a control population, the higher prevalence of maternal vitamin supplementation does not affect the internal validity of the study, but could affect the generalizability. We could also be focusing on a population with low heterogeneity in vitamin consumption and the null results in the study may be due to the select population with higher vitamin intake levels.

A few limitations arise from the lack of population-based control group. It precludes us from studying the main effects of pre-pregnancy vitamin supplementation and nutrients from diet. Although we did not find gene-environment interaction with vitamin supplementation pre-pregnancy, this does not suggest that vitamin supplementation pre-pregnancy is not related to

neuroblastoma. Only multiplicative interaction can be assessed in a case-parent triad.[359] However, additive interaction may be more biologically relevant and can influence public health decisions more, given the nature of the case-parent We are unable to code these interactions with a common referent and thus unable to discern the "baseline" risk for homozygous major alleles in each exposure group.

5.4 Implications and Conclusions

5.4.1 SNP Main effects

5.4.1.1 Previously studied SNPs

Folate from diet and SNPs in folate-related genes have been consistently linked with neural tube defects.[195,227,249] Additionally, genetic variants in the one-carbon pathway have been associated with increased plasma homocysteine levels and decreased plasma and red blood cell folate levels.[222-225,240,241] However, we did not find any associations between known folate-related SNPs and neuroblastoma. de Miranda et al. found an positive offspring association [G/A+A/A vs. G/G OR: 3.01 (95% CI: 1.06, 10.31)] between *SLC19A1* 80G>A (rs1051266) in a case-control study in Brazil comprised of 31 cases and 92 controls.[85] Montalvao-de-Azevedo et al. conducted a Brazilian mother-child dyad study of 66 case mother-child dyads and 453 control mother child dyads which replicated this offspring association [G/A+A/A vs. G/G OR: 2.51 (95% CI: 1.24, 5.08)] and found a maternal association [G/A+A/A vs. G/G OR: 3.11 (05% CI: 1.09, 8.90).[86] However, our study did not replicate these results (Appendix 3 and 4), possibly due to maternal confounding in their studies or differences in sample size and study population characteristics such as diet, race and vitamin supplementation.

Folic acid and folate has been inconsistently linked with neuroblastoma. An ecologic study demonstrated a decrease in the incidence of neuroblastoma in Ontario, Canada after folic

acid fortification. However, this study only reported 37 post-fortification cases.[99] When a similar study was conducted in the US with a larger sample in Surveillance, Epidemiology, and End Results Program, the incidence remained steady after folic acid fortification.[48] Folic acid fortification in the United States and Canada could have an appreciable effect on our results. Studies have demonstrated that *MTHFR* 667C>T has less of an effect on folate levels when folate from diet is high.[353,360] Although the effects of other one-carbon metabolism variants in relation folate consumption have not been established, it is possible any genetic effect would be diminished due the higher levels of folate due to fortification or the high level of supplementation of mothers enrolled in NENA.

5.4.1.2 Offspring and Maternal SNP Main effects

Maternal rs12442054 was selected for its proximity to *STRA6* – a retinoid transmembrane protein – and was FDR-corrected significantly associated with neuroblastoma. Additionally, the QQ plot also demonstrates that this SNP deviates from the expected normal distribution of p-values (Appendix 5). Unfortunately, the SNP is intergenic within a region of unknown function and not in high linkage disequilibrium (r^2>0.8) with any other SNPs. A study suggested that this SNP is located within non-coding RNA but this location has never been replicated and the function of this non-coding RNA is unknown. Non-coding RNA can encode for regulatory and housekeeping RNAs such as ribosomal RNA, transfer RNA and microRNAs. Studies are being conducted to determine the function of variation within these non-coding RNA regions.[361]

Neuroblastoma is clinically and biologically heterogeneous. Some cases present with aggressive disease and others with tumors that spontaneously regress with no treatment.[1,43] A risk-classification schema was defined by the COG to help with prognostication.[43] Although these categories were created for prognostic purposes, they may be etiologically relevant.

Previous studies have identified genetic variants associated with high-risk and low-risk neuroblastoma,[6,79,83] suggesting each risk-stratification might have a distinct set of underlying variants contributing to its development. One study demonstrated *MYCN* amplification status – a strong prognostic marker for high-risk neuroblastoma – does not change over time.[45] Our study further strengthens the argument that the prognostic risk-categories could be related to etiology. However, without additional studies, we cannot be sure if this is due to the sample size or the inherent heterogeneity of the disease.

We found nine offspring SNPs in or near genes related to vitamin A associated with intermediate-risk neuroblastoma. Intermediate-risk is the most clinically heterogeneous risk-classification and recent tumor genomic profiling suggests the intermediate risk-classification warrant updating.[362] Additionally, three of these SNPs were available in the CHOP case-control replication study and did not replicate NENA findings. Thus further highlighting the heterogeneity of the intermediate-risk classification and the uncertainty in the interpretation of these results.

Maternal rs6776706 near *RARB* was significantly positively associated with high-risk neuroblastoma. The promoter to *RARB* is often hyper-methylated in small cell lung cancer, prostate cancer and head and neck cancers.[363-365] Although *RARB* is not methylated in neuroblastoma cell lines and tumors,[366] there is evidence in mice and *in vitro* studies that *RARB* is involved in neuronal differentiation through retinoic acid signaling.[367,368] However, how this SNP affects *RARB* expression and the exact function of this region is unknown.

Maternal rs11103603, located in *RXRA,* was associated with infant neuroblastoma (age at diagnosis < 1 year). Variants in *RXRA* have been associated with serum vitamin D levels as well

as decreased risk of colon adenoma recurrence.[343,369] Additionally, studies have suggested that vitamin D can inhibit neuroblastoma growth in mice.[370] However, we are unable to explore the gene-environment interaction of this variant with vitamin D in NENA. Since vitamin D can be synthesized dermally from sunlight, skin color and amount of sun exposure plays a larger role in vitamin D levels than diet. [371] Even with a reliably measured diet, it would be invalid to assume that the synthesized vitamin D would be equal among all NENA mothers since families were recruited from across all of North America, encompassing many different races and geographic locations.

5.4.1.3 Gene-environment interaction

We found a FDR-corrected significant gene-environment interaction with vitamin A from diet when classified at the RDA. ADH7 is involved in the conversion of retinol to retinoic acid, as well as alcohol metabolism.[151,372,373] Mice with an *adh7* knockout have an increased risk of embryonic lethality at low levels of vitamin A, but not with sufficient intake.[374,375] SNPs located in *ADH7* have been associated with cancers with a strong alcohol component, such as squamous cell carcinoma of the head and neck and colorectal cancer.[376,377] Since mouse studies do suggest that *adh7* may be more involved with vitamin A metabolism and this present study suggests a link between neuroblastoma, vitamin A and *ADH7*, additional studies are warranted to further explore this link.[165,346]

Our results suggest that choline may play an important role in neuroblastoma development. It has been noted that during pregnancy, choline demand is high and is transported across the placenta against a concentration gradient.[378,379] Although choline can be synthesized *de novo*, diet is a major contributor to choline.[355] Choline is not typically contained in prenatal vitamins and for the few that do contain some, the amount of choline tends to be much lower

than the recommended Adequate Intake. Since the ability to synthesize choline *de novo* is dependent on gender, menopausal status and genetic variation and all women in the study are pre-menopausal, choline levels in NENA participants can be assumed to depend on genetics and diet.[277,286] Choline is synthesized *de novo* in the liver, through a process catalyzed by PEMT.[380] We did not observe any association with SNPs near or in *PEMT* and neuroblastoma. However, the candidate *PEMT* SNP rs12325817, which has been previously associated with choline levels, was unable to be genotyped due to low genotyping scores.[286] The offspring SNP is available in the CHOP replication study, and a null association was seen with offspring rs12325817 (OR: 0.98) and neuroblastoma. However, since choline is transmitted to the fetus in utero, further studies with maternal variants should be studied.

Two of the gene-environment interactions in NENA (vitamin A dichotomized at the RDA and choline dichotomized at the Adequate Intake) are "pure" interactions in that the genetic effect crosses the null between the two exposure states. Such "pure" interactions tend to work against the detection of marginal associations for genetic effects. Although "pure" interactions can occur, only a few examples have been consistently replicated in epidemiologic studies.[381-384] Moreover, the function of these two SNPs and gene regions are unknown, and our results should be interpreted with caution.

5.4.2 Consideration for Future Studies

Neuroblastoma GWA case-control studies found SNPs that are associated with neuroblastoma.[6,7] However, like many other GWA studies of complex diseases, these SNPs are likely to individually contribute little to the development of neuroblastoma.[385] The underlying hypothesis of GWA studies is "common disease, common variant" or that if the disease is common in the population (1-10%) and heritable, the variant will also be common in the

population.[386] GWA study SNP arrays, which are designed to capture common genetic variation, would not be as appropriate for neuroblastoma to find large effect sizes.[299] However, common variants likely have small effect sizes, but could be involved with gene-environment interaction where certain subgroups have large effect sizes. Some sequencing has been done with case-control studies and neuroblastoma with promising results that merit further studies of rare variants.[84]

We found some interesting results with maternal variants, which warrant additional study and replication. Future studies should consider designs that can study maternal associations with rare variants as well as interaction with other maternal exposures.[21,317,387] Maternal environment exposures, maternal genotype and offspring genotype all contribute to the fetal environment. The fetal environment is important to the development and malignant transformation of neuroblastoma. Associations have been found with maternal environmental exposures and offspring genotype,[7,80,106,110,113,119,121,385] but few have studied maternal genotype and neuroblastoma.[86] Maternal variants may be important to cancers that have early life origins such as childhood acute lymphoblastic leukemia[352,388] and medulloblastoma.[389] In addition to replicating our results, future studies can focus on maternal variants that in pathways that been previously associated with neuroblastoma such as genes related to maternal metabolism or detoxification of painkillers and occupational exposures linked to neuroblastoma.

Family-based studies also allow for the assessment of parent-of-origin effects, including imprinting.[390] If not properly accounted for, such effects can mask associations. Imprinted genes have been implicated with common diseases such as autism, breast cancer and diabetes.[391] The genes that were genotyped in NENA have no evidence of imprinting. We are also not powered to look at imprinting effects without an *a prior* hypothesis.[392] However, there are few population

based studies with parental data available and as more genetic research is conducted in neuroblastoma, it could be worthwhile to explore imprinting the NENA.

Our independent replication study only had offspring genotyping. Few offspring SNPs in NENA were significant and these did not replicate in CHOP. A few maternal variants within this study were significant, and should be replicated and functionality should be further explored with mice and *in vitro* studies. All the FDR-corrected significant SNPs were in non-coding regions. Intronic SNPs are known to affect splicing and intergenic SNPs can code for intergenic transcription factor binding sites or non-coding RNA.[338] A few the significant SNPs are located in intergenic regions that may code for transcription factors, but these have not been replicated.[393] Additionally, we were not able to capture the candidate *PEMT* variant due to the limitations of the genotyping chip in NENA. Given the suggestive maternal gene-choline interaction, future studies, including NENA, can explore choline though synthesis *de no*vo and diet.

5.4.3 Public Health Implications

Genetic studies have plagued with the "missing heritability" problem.[394] GWA studies have failed to identify the variants that contribute the most to the heritability of complex diseases.[394] This lack of heritability could be explained by gene-environment or gene-gene interactions in which the variants themselves do not have an appreciable marginal effect. Moreover, gene-environment interaction studies allow for the discovery of a genetic subpopulation susceptible to environment hazards. This information could further inform risk prediction models and have implications for personalized medicine.[395] If there is no an adverse effect of the "environment" variable, gene-environment interaction could inform dietary recommendations.

This study suggests that maternal pre-pregnancy vitamin supplementation or folic acid and folate from diet do not multiplicatively modify the effects on neuroblastoma risks of SNPs that are in vitamin A, choline and folate pathways. In the era of folic acid fortification it is feasible that maternal pre-pregnancy vitamin supplementation or folate does not modify the effects of other SNPs that have been previously associated with neuroblastoma.

While folic acid is beneficial to the prevention of neural tube defects, [93,195] our null associations seen with SNPs that are known to modify maternal serum folate levels suggest that folate may not play a large role in neuroblastoma development. However, this does not preclude the recommendation of prenatal vitamins for women of child bearing age or during pregnancy due to their protective effect for other outcomes. Although one study should not prompt any wide sweeping policy changes, this study does highlight the need for further studies into vitamin A and choline in relation to neuroblastoma. Vitamin A is used in the treatment of neuroblastoma and has potential importance with the development of neuroblastoma.[170,171] Choline has only recently been identified as a necessary nutrient for pregnant women because of its role in fetal development.[18] Additional studies should be conducted elucidating the effect of choline and vitamin A on fetal and neuronal development.

5.5 Summary

This study evaluated associations between maternal and offspring variants in vitamin A, choline and folate-related genes and gene-environment interaction in case-parent triads. Overall, these analyses suggest that folate is not as important to the risk of neuroblastoma as it is to birth defects or other childhood cancers. There is a potential for interaction with certain SNPs and choline from diet that warrants additional larger studies to further confirm the interaction. SNPs in vitamin A-related genes may be related to risk of neuroblastoma and such a role is supported

by relevant biologic plausibility. Since we are the first study to look into this hypothesis, our results do warrant replication and further attempts to characterize the interactions between gene variants and vitamin consumption.

APPENDIX 1. RESULTS FROM OFFSPRING VITAMIN A-RELATED SNPS IN NENA AND CHOP REPLICATION STUDY

SNP	Gene	NENA					CHOP				
		Minor Allele	Major Allele	RR (95% CI)	P-value	FDR Q-value	Minor Allele	Major Allele	OR (95% CI)	P-value	FDR Q-value
rs4842196	*RXRA*	C	A	1.30(1.08, 1.57)	0.006	0.833	--	--	--	--	--
rs4699720	*ADH4*	C	T	1.30(1.07, 1.58)	0.008	0.833	T	C	0.98(0.90, 1.08)	0.709	>0.999
rs4699710	*ADH4*	C	T	1.27(1.06, 1.52)	0.010	0.833	T	C	0.97(0.90, 1.06)	0.536	>0.999
rs4646684	*ALDH1A3*	A	G	0.81(0.68, 0.96)	0.014	0.833	G	A	0.96(0.88, 1.03)	0.263	>0.999
rs1007971	*RXRA*	G	C	1.28(1.05, 1.56)	0.015	0.833	--	--	--	--	--
rs1229977	*ADH1A*	T	C	0.78(0.63, 0.95)	0.016	0.833	C	T	1.04(0.95, 1.15)	0.384	>0.999
rs284792	*ADH7*	A	G	1.42(1.07, 1.89)	0.016	0.833	T	C	1.09(0.95, 1.25)	0.236	>0.999
rs6771831	*RBP2*	A	G	1.22(1.03, 1.45)	0.021	0.833	A	G	0.95(0.88, 1.03)	0.26	>0.999
rs12730752	*CRABP2*	T	C	1.22(1.03, 1.44)	0.024	0.833	T	C	0.98(0.90, 1.07)	0.623	>0.999
rs2462936	*RDH5*	T	C	0.79(0.64, 0.97)	0.024	0.833	--	--	--	--	--
rs11170466	*RARG*	A	G	1.53(1.05, 2.21)	0.026	0.833	--	--	--	--	--
rs3118523	*RXRA*	G	A	1.26(1.03, 1.55)	0.026	0.833	--	--	--	--	--
rs12512110	*ADH1A*	T	G	0.70(0.52, 0.96)	0.026	0.833	T	G	1.04(0.90, 1.20)	0.588	>0.999
rs7670060	*ADH4*	T	G	1.24(1.02, 1.50)	0.029	0.833	T	G	1.05(0.97, 1.15)	0.226	>0.999
rs167187	*RBP1*	G	A	1.20(1.01, 1.42)	0.034	0.833	A	G	1.05(0.96, 1.13)	0.278	>0.999
rs16844995	*RXRG*	C	T	1.25(1.02, 1.54)	0.034	0.833	C	T	0.93(0.84, 1.03)	0.194	>0.999
rs2156731	*ADH4*	A	G	0.72(0.53, 0.98)	0.037	0.833	T	C	1.03(0.89, 1.19)	0.679	>0.999
rs7959622	*RDH5*	C	T	1.50(1.02, 2.21)	0.040	0.833	--	--	--	--	--
rs2364120	*RARB*	G	A	1.37(1.01, 1.85)	0.042	0.833	A	G	0.96(0.84, 1.10)	0.563	>0.999
rs100537	*RXRG*	A	G	1.19(1.01, 1.40)	0.044	0.833	G	A	1.02(0.94, 1.11)	0.585	>0.999
rs1730221	*RARB*	G	C	1.20(1.01, 1.43)	0.044	0.833	G	C	0.99(0.91, 1.07)	0.77	>0.999
rs4889291	*BCMO1*	G	A	0.84(0.71, 1.00)	0.046	0.833	G	A	0.96(0.88, 1.05)	0.349	>0.999
rs8187945	*ALDH1A1*	T	C	1.48(1.00, 2.18)	0.049	0.833	A	G	0.88(0.73, 1.06)	0.178	>0.999
rs283690	*RXRG*	G	A	1.18(1.00, 1.39)	0.052	0.833	A	G	0.99(0.92, 1.07)	0.871	>0.999
rs11707637	*RARB*	G	A	1.18(1.00, 1.40)	0.056	0.833	G	A	1.03(0.95, 1.11)	0.523	>0.999
rs4646678	*ALDH1A3*	T	C	1.23(0.99, 1.53)	0.056	0.833	T	C	1.01(0.91, 1.11)	0.912	>0.999
rs6795340	*RARB*	A	G	1.20(0.99, 1.46)	0.058	0.833	A	G	1.00(0.91, 1.09)	0.983	>0.999
rs1045570	*RXRA*	T	G	1.23(0.99, 1.53)	0.059	0.833	--	--	--	--	--
rs11264527	*CRABP2*	C	T	1.17(0.99, 1.39)	0.062	0.833	T	C	1.01(0.93, 1.10)	0.79	>0.999
rs455696	*RXRG*	C	T	1.20(0.99, 1.46)	0.069	0.833	A	G	1.01(0.91, 1.11)	0.907	>0.999
rs1805343	*RXRA*	G	A	1.17(0.99, 1.39)	0.071	0.833	--	--	--	--	--

RR: Risk Ratio; **CI**: Confidence Interval; **OR**: Odds Ratio; --: Unavailable in replication study

SNP	Gene	NENA					CHOP				
		Minor Allele	Major Allele	RR (95% CI)	P-value	FDR Q-value	Minor Allele	Major Allele	OR (95% CI)	P-value	FDR Q-value
rs4646669	*ALDH1A3*	T	C	1.23(0.98, 1.53)	0.072	0.833	T	C	1.01(0.90, 1.12)	0.911	>0.999
rs283697	*RXRG*	A	C	0.83(0.67, 1.02)	0.072	0.833	C	A	1.00(0.91, 1.10)	0.99	>0.999
rs6767543	*RARB*	G	A	0.85(0.71, 1.02)	0.078	0.833	A	G	0.98(0.90, 1.07)	0.614	>0.999
rs3138136	*RDH5*	A	G	1.29(0.97, 1.70)	0.078	0.833	T	C	1.04(0.92, 1.18)	0.53	>0.999
rs6774691	*RBP2*	A	G	1.26(0.97, 1.64)	0.080	0.833	A	G	0.88(0.77, 1.00)	0.046	>0.999
rs12906432	*ALDH1A3*	T	G	0.84(0.69, 1.02)	0.083	0.833	--	--	--	--	--
rs3767343	*RXRG*	A	G	1.16(0.98, 1.37)	0.085	0.833	A	G	0.99(0.92, 1.07)	0.814	>0.999
rs4266713	*ALDH1A1*	A	T	0.79(0.61, 1.04)	0.087	0.833	A	T	1.00(0.89, 1.13)	0.977	>0.999
rs2715553	*RARA*	C	T	0.87(0.74, 1.02)	0.087	0.833	A	G	0.99(0.92, 1.07)	0.838	>0.999
rs1154473	*ADH7*	T	C	1.15(0.98, 1.35)	0.089	0.833	G	A	1.05(0.96, 1.14)	0.3	>0.999
rs11917304	*RARB*	C	T	1.22(0.97, 1.55)	0.090	0.833	C	T	1.02(0.91, 1.15)	0.691	>0.999
rs3772868	*RBP1*	T	C	1.24(0.97, 1.59)	0.091	0.833	A	G	0.99(0.88, 1.11)	0.862	>0.999
rs748964	*RXRA*	C	G	1.22(0.97, 1.54)	0.093	0.833	--	--	--	--	--
rs6564859	*BCMO1*	G	A	1.17(0.97, 1.40)	0.094	0.833	G	A	1.08(0.99, 1.18)	0.081	>0.999
rs11204208	*RBP3*	T	G	1.26(0.96, 1.65)	0.096	0.833	T	G	0.92(0.80, 1.05)	0.213	>0.999
rs2413292	*ISX*	T	C	1.18(0.97, 1.44)	0.096	0.833	T	C	1.01(0.92, 1.11)	0.803	>0.999
rs6909923	*ALDH8A1*	G	A	1.31(0.95, 1.81)	0.096	0.833	G	A	1.03(0.88, 1.20)	0.742	>0.999
rs6803265	*RARB*	A	T	1.21(0.97, 1.51)	0.097	0.833	A	T	0.93(0.84, 1.03)	0.184	>0.999
rs2072827	*ALDH8A1*	A	G	0.87(0.74, 1.03)	0.099	0.833	A	G	1.00(0.92, 1.09)	0.961	>0.999
rs10009145	*ADH4*	A	G	0.87(0.73, 1.03)	0.100	0.833	A	G	0.96(0.89, 1.04)	0.342	>0.999
rs41419946	*RXRG*	T	A	1.32(0.95, 1.84)	0.103	0.839	T	A	1.03(0.88, 1.20)	0.709	>0.999
rs4657438	*RXRG*	C	A	0.78(0.57, 1.06)	0.106	0.839	C	A	1.15(0.98, 1.35)	0.097	>0.999
rs1864907	*RARB*	G	A	1.34(0.94, 1.92)	0.106	0.839	--	--	--	--	--
rs1800759	*ADH4*	A	C	1.15(0.97, 1.36)	0.110	0.842	G	T	0.96(0.89, 1.04)	0.341	>0.999
rs6762247	*RARB*	T	C	0.82(0.64, 1.05)	0.112	0.842	T	C	1.01(0.89, 1.15)	0.842	>0.999
rs41356949	*RBP2*	T	C	0.79(0.60, 1.06)	0.113	0.842	T	C	1.11(0.97, 1.28)	0.139	>0.999
rs913422	*CYP26A1*	C	T	0.87(0.74, 1.03)	0.115	0.842	G	A	0.94(0.86, 1.02)	0.145	>0.999
rs482284	*RARA*	A	G	1.15(0.97, 1.38)	0.118	0.850	G	A	1.03(0.94, 1.12)	0.557	>0.999
rs4681063	*RARB*	C	T	0.87(0.73, 1.04)	0.122	0.860	C	T	1.03(0.95, 1.12)	0.464	>0.999
rs7905501	*CYP26A1*	T	C	1.18(0.96, 1.47)	0.123	0.860	T	C	0.96(0.87, 1.06)	0.473	>0.999
rs11580324	*CRABP2*	C	G	1.17(0.96, 1.44)	0.129	0.870	C	G	1.15(1.01, 1.29)	0.028	>0.999
rs904092	*ADH1A*	A	G	0.84(0.67, 1.05)	0.131	0.870	G	A	1.02(0.92, 1.14)	0.668	>0.999
rs1229966	*ADH1A*	C	T	1.14(0.96, 1.35)	0.134	0.870	G	A	0.97(0.89, 1.05)	0.406	>0.999
rs9879736	*RBP1*	T	C	1.19(0.95, 1.50)	0.137	0.870	C	T	1.09(0.98, 1.22)	0.125	>0.999
rs6564863	*BCMO1*	T	C	0.88(0.73, 1.04)	0.138	0.870	C	T	0.99(0.91, 1.07)	0.745	>0.999

RR: Risk Ratio; **CI**: Confidence Interval; **OR**: Odds Ratio; --: Unavailable in replication study

SNP	Gene	NENA					CHOP				
		Minor Allele	Major Allele	RR (95% CI)	P-value	FDR Q-value	Minor Allele	Major Allele	OR (95% CI)	P-value	FDR Q-value
rs3773438	*RARB*	A	G	1.20(0.94, 1.54)	0.142	0.870	T	C	0.96(0.85, 1.07)	0.435	>0.999
rs7235277	*TTR*	C	G	1.14(0.96, 1.36)	0.146	0.870	C	G	1.04(0.96, 1.13)	0.376	>0.999
rs4240705	*RXRA*	G	A	1.13(0.96, 1.34)	0.148	0.870	--	--	--	--	--
rs285428	*RXRG*	C	T	0.85(0.68, 1.06)	0.150	0.870	C	T	1.12(1.00, 1.26)	0.051	>0.999
rs1154460	*ADH7*	A	G	0.89(0.75, 1.04)	0.151	0.870	A	G	1.05(0.97, 1.13)	0.244	>0.999
rs1902715	*RBP3*	A	G	1.17(0.94, 1.45)	0.154	0.870	T	C	0.97(0.88, 1.08)	0.603	>0.999
rs1108197	*RBP4*	A	G	0.89(0.75, 1.05)	0.154	0.870	A	G	0.97(0.89, 1.05)	0.405	>0.999
rs11264518	*CRABP2*	T	C	1.13(0.96, 1.34)	0.154	0.870	T	C	0.99(0.92, 1.08)	0.864	>0.999
rs2120200	*RARA*	G	A	1.21(0.93, 1.56)	0.158	0.870	G	A	0.97(0.84, 1.11)	0.615	>0.999
rs1286773	*RARB*	G	C	0.84(0.66, 1.07)	0.159	0.870	G	C	0.98(0.87, 1.10)	0.695	>0.999
rs1286650	*RARB*	A	T	1.13(0.95, 1.33)	0.161	0.870	T	A	0.99(0.92, 1.08)	0.888	>0.999
rs955243	*LRAT*	A	G	0.89(0.76, 1.05)	0.170	0.870	G	A	1.02(0.94, 1.10)	0.615	>0.999
rs17016570	*RARB*	G	A	1.26(0.90, 1.76)	0.172	0.870	G	A	0.90(0.77, 1.05)	0.174	>0.999
rs2116703	*RARB*	A	G	1.16(0.94, 1.44)	0.172	0.870	A	G	0.91(0.82, 1.01)	0.075	>0.999
rs157862	*RXRG*	T	A	1.17(0.93, 1.47)	0.175	0.870	T	A	1.04(0.92, 1.17)	0.531	>0.999
rs7428398	*RBP1*	A	G	0.82(0.62, 1.09)	0.175	0.870	A	G	1.10(0.96, 1.26)	0.183	>0.999
rs211585	*RBP1*	C	T	0.89(0.76, 1.05)	0.179	0.870	C	T	1.02(0.94, 1.10)	0.682	>0.999
rs1371338	*RBP2*	C	T	0.89(0.76, 1.05)	0.180	0.870	A	G	0.99(0.92, 1.07)	0.79	>0.999
rs13120304	*ADH1A*	A	T	1.13(0.95, 1.34)	0.180	0.870	A	T	1.04(0.96, 1.13)	0.291	>0.999
rs755661	*RARB*	T	C	1.12(0.95, 1.33)	0.183	0.870	C	T	0.92(0.85, 0.99)	0.035	>0.999
rs17587689	*ADH7*	A	G	1.16(0.93, 1.45)	0.186	0.870	A	G	0.96(0.86, 1.06)	0.427	>0.999
rs1123944	*RXRG*	T	C	1.17(0.93, 1.46)	0.187	0.870	A	G	0.98(0.88, 1.10)	0.757	>0.999
rs10882273	*RBP4*	C	T	1.12(0.95, 1.34)	0.187	0.870	C	T	1.00(0.92, 1.09)	0.957	>0.999
rs5750041	*ISX*	T	C	1.16(0.93, 1.46)	0.188	0.870	T	C	0.96(0.86, 1.07)	0.448	>0.999
rs4144005	*ALDH1A2*	T	C	0.89(0.75, 1.06)	0.188	0.870	T	C	0.99(0.92, 1.07)	0.829	>0.999
rs991316	*ADH7*	A	G	0.89(0.75, 1.06)	0.192	0.870	C	T	0.99(0.92, 1.08)	0.888	>0.999
rs17016773	*RARB*	T	C	1.15(0.93, 1.42)	0.194	0.870	T	C	1.07(0.97, 1.18)	0.207	>0.999
rs10885982	*PNLIP*	A	G	1.21(0.91, 1.61)	0.195	0.870	A	G	1.12(0.96, 1.31)	0.134	>0.999
rs3818730	*RXRA*	A	G	0.89(0.74, 1.06)	0.195	0.870	A	G	1.03(0.95, 1.12)	0.495	>0.999
rs9934274	*BCMO1*	G	C	1.12(0.94, 1.32)	0.197	0.870	G	C	1.04(0.96, 1.13)	0.314	>0.999
rs2602884	*ADH4*	C	T	1.17(0.92, 1.48)	0.200	0.870	T	C	1.00(0.90, 1.11)	0.999	>0.999
rs10776909	*RXRA*	T	C	1.14(0.93, 1.39)	0.204	0.870	C	T	1.00(0.91, 1.10)	0.976	>0.999
rs12512714	*LRAT*	G	C	1.12(0.94, 1.33)	0.206	0.870	G	C	1.00(0.92, 1.08)	0.99	>0.999
rs9886504	*RDH10*	A	G	1.15(0.93, 1.42)	0.206	0.870	A	G	0.94(0.85, 1.03)	0.183	>0.999
rs2071025	*RXRB*	C	T	0.88(0.73, 1.07)	0.207	0.870	G	A	0.98(0.90, 1.07)	0.679	>0.999

RR: Risk Ratio; **CI**: Confidence Interval; **OR**: Odds Ratio; --: Unavailable in replication study

SNP	Gene	NENA					CHOP				
		Minor Allele	Major Allele	RR (95% CI)	P-value	FDR Q-value	Minor Allele	Major Allele	OR (95% CI)	P-value	FDR Q-value
rs1153592	*RARB*	A	T	0.87(0.69, 1.08)	0.208	0.870	A	T	0.98(0.87, 1.09)	0.659	>0.999
rs1153606	*RARB*	G	A	0.88(0.71, 1.08)	0.212	0.878	G	A	0.97(0.88, 1.07)	0.548	>0.999
rs11856111	*CRABP1*	C	T	1.12(0.94, 1.35)	0.216	0.879	C	T	1.03(0.95, 1.12)	0.447	>0.999
rs994772	*ADH7*	A	G	0.85(0.66, 1.10)	0.220	0.879	T	C	0.98(0.87, 1.11)	0.797	>0.999
rs7620632	*RARB*	C	T	0.86(0.68, 1.10)	0.227	0.879	C	T	0.86(0.77, 0.96)	0.01	>0.999
rs1881705	*RARB*	G	A	0.90(0.76, 1.07)	0.229	0.879	T	C	0.96(0.88, 1.04)	0.278	>0.999
rs970902	*RXRB*	G	A	0.91(0.77, 1.06)	0.229	0.879	T	C	1.03(0.95, 1.11)	0.513	>0.999
rs1286738	*RARB*	T	C	1.13(0.93, 1.38)	0.230	0.879	T	C	1.02(0.93, 1.12)	0.705	>0.999
rs729147	*ADH7*	G	A	0.89(0.73, 1.08)	0.237	0.879	A	G	0.96(0.87, 1.05)	0.368	>0.999
rs7169439	*ALDH1A2*	A	G	1.17(0.90, 1.52)	0.239	0.879	--	--	--	--	--
rs12573026	*RBP4*	C	T	1.16(0.91, 1.47)	0.240	0.879	--	--	--	--	--
rs11776584	*RDH10*	A	G	1.13(0.92, 1.38)	0.241	0.879	A	G	1.06(0.96, 1.16)	0.238	>0.999
rs3772879	*RBP2*	T	A	1.17(0.90, 1.52)	0.243	0.879	A	T	1.01(0.89, 1.14)	0.862	>0.999
rs1372369	*ALDH1A2*	C	A	0.91(0.77, 1.07)	0.244	0.879	G	T	0.97(0.89, 1.05)	0.417	>0.999
rs6564854	*BCMO1*	G	A	1.11(0.93, 1.33)	0.247	0.879	G	A	1.07(0.98, 1.16)	0.13	>0.999
rs2899611	*ALDH1A2*	G	T	0.91(0.77, 1.07)	0.247	0.879	G	T	1.01(0.93, 1.10)	0.765	>0.999
rs4681027	*RARB*	G	T	1.23(0.86, 1.76)	0.250	0.879	G	T	1.02(0.84, 1.23)	0.836	>0.999
rs3817776	*ALDH8A1*	C	T	1.10(0.93, 1.30)	0.251	0.879	T	C	1.00(0.92, 1.08)	0.936	>0.999
rs12739596	*RXRG*	C	A	0.89(0.72, 1.09)	0.253	0.879	C	A	1.05(0.96, 1.15)	0.309	>0.999
rs3852534	*RDH5*	A	G	1.10(0.93, 1.30)	0.253	0.879	--	--	--	--	--
rs8187876	*ALDH1A1*	A	G	1.20(0.88, 1.64)	0.259	0.879	T	C	0.99(0.84, 1.17)	0.904	>0.999
rs12648206	*ADH7*	G	A	0.89(0.73, 1.09)	0.260	0.879	G	A	0.93(0.84, 1.02)	0.117	>0.999
rs17016778	*RARB*	G	A	1.11(0.92, 1.35)	0.263	0.879	G	A	1.06(0.96, 1.16)	0.263	>0.999
rs9821204	*RBP1*	A	C	0.89(0.73, 1.09)	0.264	0.879	A	C	1.04(0.94, 1.14)	0.468	>0.999
rs7187507	*BCMO1*	T	A	1.10(0.93, 1.31)	0.266	0.879	A	T	0.97(0.89, 1.05)	0.477	>0.999
rs2899240	*ISX*	G	A	0.91(0.76, 1.08)	0.267	0.879	A	G	0.99(0.92, 1.08)	0.898	>0.999
rs7071684	*RBP3*	T	C	1.11(0.93, 1.32)	0.269	0.879	T	C	0.93(0.85, 1.01)	0.103	>0.999
rs6518932	*ISX*	T	C	0.89(0.72, 1.10)	0.270	0.879	T	C	1.06(0.96, 1.18)	0.274	>0.999
rs1286658	*RARB*	T	C	1.16(0.89, 1.52)	0.270	0.879	C	T	0.99(0.88, 1.13)	0.923	>0.999
rs1153603	*RARB*	A	G	0.91(0.76, 1.08)	0.276	0.879	T	C	1.00(0.92, 1.09)	0.92	>0.999
rs2925455	*RDH10*	C	A	0.82(0.57, 1.18)	0.279	0.879	C	A	1.08(0.90, 1.29)	0.407	>0.999
rs9835241	*RBP1*	G	A	1.11(0.92, 1.35)	0.280	0.879	G	A	1.00(0.91, 1.09)	0.992	>0.999
rs3758495	*RBP3*	A	G	0.87(0.68, 1.12)	0.281	0.879	G	A	1.07(0.95, 1.21)	0.277	>0.999
rs11865869	*BCMO1*	G	A	0.90(0.74, 1.09)	0.286	0.879	G	A	0.96(0.88, 1.06)	0.422	>0.999
rs7080494	*CYP26A1*	G	A	1.10(0.92, 1.31)	0.286	0.879	A	G	0.98(0.90, 1.07)	0.726	>0.999

RR: Risk Ratio; **CI**: Confidence Interval; **OR**: Odds Ratio; --: Unavailable in replication study

SNP	Gene	NENA					CHOP				
		Minor Allele	Major Allele	RR (95% CI)	P-value	FDR Q-value	Minor Allele	Major Allele	OR (95% CI)	P-value	FDR Q-value
rs3118529	*RXRA*	C	T	1.10(0.92, 1.31)	0.287	0.879	T	C	1.09(1.00, 1.19)	0.061	>0.999
rs1286730	*RARB*	G	C	1.14(0.90, 1.46)	0.287	0.879	G	C	1.00(0.89, 1.12)	0.961	>0.999
rs9373116	*ALDH8A1*	C	G	1.09(0.93, 1.29)	0.296	0.879	G	C	1.01(0.93, 1.10)	0.763	>0.999
rs156500	*LRAT*	C	A	0.88(0.68, 1.13)	0.300	0.879	G	T	0.98(0.86, 1.11)	0.698	>0.999
rs11187549	*RBP4*	G	A	1.15(0.88, 1.51)	0.301	0.879	--	--	--	--	--
rs1286750	*RARB*	C	A	0.91(0.75, 1.09)	0.301	0.879	C	A	0.94(0.86, 1.03)	0.197	>0.999
rs3819197	*ADH1A*	T	C	1.11(0.91, 1.34)	0.308	0.879	T	C	0.96(0.88, 1.06)	0.429	>0.999
rs3767342	*RXRG*	C	T	1.13(0.89, 1.44)	0.310	0.879	C	T	1.00(0.89, 1.13)	0.937	>0.999
rs3821629	*RARB*	G	A	1.11(0.91, 1.34)	0.310	0.879	C	T	0.95(0.86, 1.04)	0.252	>0.999
rs7541159	*RXRG*	T	G	1.09(0.92, 1.29)	0.312	0.879	G	T	0.97(0.90, 1.05)	0.489	>0.999
rs6776706	*RARB*	A	T	1.09(0.92, 1.31)	0.324	0.879	A	T	1.01(0.93, 1.10)	0.745	>0.999
rs1465057	*RARG*	C	T	0.87(0.67, 1.14)	0.325	0.879	C	T	1.10(0.96, 1.25)	0.171	>0.999
rs17029657	*RARB*	G	T	1.10(0.91, 1.33)	0.325	0.879	G	T	1.06(0.97, 1.17)	0.173	>0.999
rs1538648	*CYP26C1*	C	T	0.92(0.78, 1.09)	0.327	0.879	G	A	0.97(0.89, 1.05)	0.46	>0.999
rs6580936	*RARG*	G	A	1.11(0.90, 1.37)	0.331	0.879	G	A	1.00(0.90, 1.11)	0.99	>0.999
rs11103473	*RXRA*	T	A	1.09(0.92, 1.28)	0.331	0.879	A	T	1.06(0.97, 1.15)	0.229	>0.999
rs9871002	*RARB*	T	A	0.89(0.70, 1.13)	0.332	0.879	T	A	0.89(0.79, 0.99)	0.04	>0.999
rs12502290	*ADH7*	A	G	0.92(0.77, 1.09)	0.333	0.879	A	G	0.97(0.90, 1.06)	0.55	>0.999
rs17108978	*RBP4*	A	G	1.10(0.91, 1.32)	0.334	0.879	A	G	1.01(0.93, 1.10)	0.808	>0.999
rs1128977	*RXRG*	T	C	1.09(0.92, 1.30)	0.335	0.879	A	G	0.99(0.91, 1.07)	0.77	>0.999
rs752739	*RXRG*	T	C	0.91(0.75, 1.11)	0.336	0.879	A	G	1.02(0.92, 1.12)	0.741	>0.999
rs4646607	*ALDH1A2*	T	G	1.09(0.92, 1.28)	0.339	0.879	A	C	1.00(0.92, 1.08)	0.999	>0.999
rs11214139	*BCO2*	G	A	0.88(0.68, 1.14)	0.339	0.879	G	A	0.99(0.87, 1.11)	0.824	>0.999
rs157861	*RXRG*	G	C	1.11(0.90, 1.36)	0.340	0.879	G	C	1.03(0.93, 1.13)	0.603	>0.999
rs974456	*STRA6*	T	C	1.09(0.91, 1.32)	0.343	0.879	T	C	1.02(0.93, 1.13)	0.653	>0.999
rs4148887	*ADH4*	C	T	0.89(0.69, 1.14)	0.347	0.879	G	A	0.96(0.85, 1.08)	0.48	>0.999
rs11898950	*CYP26B1*	G	A	0.91(0.75, 1.11)	0.348	0.879	--	--	--	--	--
rs3935542	*CRABP2*	G	C	0.92(0.77, 1.10)	0.350	0.879	C	G	0.93(0.86, 1.02)	0.116	>0.999
rs3138142	*RDH5*	A	G	1.10(0.90, 1.35)	0.351	0.879	--	--	--	--	--
rs8181419	*RBP4*	G	T	1.12(0.89, 1.41)	0.352	0.879	G	T	0.99(0.89, 1.10)	0.88	>0.999
rs10910	*STRA6*	G	A	1.09(0.91, 1.29)	0.355	0.879	T	C	0.99(0.91, 1.08)	0.878	>0.999
rs10110749	*RDH10*	G	C	1.08(0.92, 1.27)	0.362	0.879	G	C	0.99(0.91, 1.07)	0.727	>0.999
rs2017543	*ISX*	C	T	0.88(0.67, 1.16)	0.363	0.879	C	T	1.08(0.95, 1.23)	0.259	>0.999
rs3806412	*CRABP2*	G	T	1.08(0.91, 1.29)	0.363	0.879	T	G	1.01(0.93, 1.09)	0.873	>0.999
rs1286654	*RARB*	T	G	1.09(0.91, 1.31)	0.364	0.879	A	C	0.97(0.89, 1.06)	0.454	>0.999

RR: Risk Ratio; **CI**: Confidence Interval; **OR**: Odds Ratio; --: Unavailable in replication study

SNP	Gene	NENA					CHOP				
		Minor Allele	Major Allele	RR (95% CI)	P-value	FDR Q-value	Minor Allele	Major Allele	OR (95% CI)	P-value	FDR Q-value
rs1286664	*RARB*	T	C	0.91(0.73, 1.12)	0.366	0.879	T	C	1.01(0.92, 1.12)	0.777	>0.999
rs3758494	*RBP3*	G	C	1.10(0.90, 1.35)	0.368	0.879	G	C	0.98(0.89, 1.08)	0.672	>0.999
rs6738598	*CYP26B1*	G	A	1.17(0.83, 1.63)	0.371	0.879	G	A	0.99(0.84, 1.17)	0.908	>0.999
rs149225	*LRAT*	C	A	1.08(0.91, 1.28)	0.380	0.879	G	T	0.98(0.90, 1.06)	0.582	>0.999
rs12256889	*CYP26C1*	A	C	0.93(0.78, 1.10)	0.382	0.879	C	A	0.92(0.84, 1.00)	0.055	>0.999
rs3810619	*ISX*	T	C	0.92(0.77, 1.11)	0.382	0.879	C	T	1.06(0.98, 1.16)	0.159	>0.999
rs913423	*CYP26A1*	C	T	1.08(0.91, 1.28)	0.382	0.879	A	G	1.00(0.93, 1.08)	0.949	>0.999
rs6669441	*RXRG*	A	G	1.10(0.89, 1.34)	0.383	0.879	A	G	0.99(0.89, 1.09)	0.787	>0.999
rs361741	*ISX*	T	C	1.08(0.91, 1.27)	0.384	0.879	A	G	0.94(0.87, 1.01)	0.106	>0.999
rs1946518	*BCO2*	T	G	0.93(0.79, 1.10)	0.387	0.879	G	T	1.03(0.95, 1.12)	0.472	>0.999
rs11187519	*RBP4*	A	C	1.13(0.86, 1.47)	0.389	0.879	A	C	0.96(0.85, 1.08)	0.489	>0.999
rs2017362	*ALDH1A1*	T	C	0.93(0.78, 1.10)	0.390	0.879	T	C	0.94(0.87, 1.02)	0.163	>0.999
rs10918179	*RXRG*	A	C	1.08(0.91, 1.28)	0.390	0.879	C	A	0.99(0.91, 1.07)	0.755	>0.999
rs10800091	*RXRG*	G	A	0.93(0.79, 1.10)	0.391	0.879	G	A	1.03(0.95, 1.11)	0.524	>0.999
rs17016718	*RARB*	C	T	1.10(0.88, 1.37)	0.393	0.879	C	T	0.99(0.89, 1.10)	0.836	>0.999
rs6799734	*RARB*	C	G	0.93(0.79, 1.10)	0.394	0.879	C	G	1.03(0.94, 1.12)	0.549	>0.999
rs7629902	*RARB*	A	G	1.11(0.87, 1.42)	0.395	0.879	A	G	1.10(0.98, 1.23)	0.105	>0.999
rs10032099	*ADH4*	G	A	1.09(0.90, 1.32)	0.395	0.879	G	A	1.02(0.93, 1.12)	0.723	>0.999
rs12442054	*STRA6*	A	G	0.89(0.68, 1.16)	0.396	0.879	A	G	1.09(0.95, 1.24)	0.207	>0.999
rs7663410	*ADH7*	C	A	1.10(0.88, 1.38)	0.399	0.879	C	A	0.92(0.83, 1.01)	0.094	>0.999
rs7620852	*RARB*	C	T	0.91(0.73, 1.13)	0.399	0.879	C	T	1.07(0.96, 1.19)	0.198	>0.999
rs5755550	*ISX*	C	T	1.08(0.91, 1.27)	0.404	0.879	T	C	1.00(0.93, 1.08)	0.94	>0.999
rs17117895	*RDH5*	T	C	0.85(0.59, 1.24)	0.406	0.879	T	C	1.07(0.89, 1.28)	0.471	>0.999
rs1881704	*RARB*	G	C	1.12(0.86, 1.45)	0.408	0.879	C	G	1.04(0.92, 1.17)	0.574	>0.999
rs348458	*ALDH1A1*	A	G	0.93(0.79, 1.10)	0.409	0.879	T	C	0.94(0.87, 1.02)	0.131	>0.999
rs11926758	*RARB*	T	G	1.14(0.83, 1.57)	0.410	0.879	T	G	1.11(0.96, 1.30)	0.168	>0.999
rs1506951	*RXRG*	T	C	0.91(0.73, 1.14)	0.410	0.879	A	G	1.00(0.89, 1.12)	0.956	>0.999
rs7624894	*RARB*	C	T	1.12(0.86, 1.45)	0.415	0.879	C	T	0.94(0.82, 1.08)	0.398	>0.999
rs12934922	*BCMO1*	T	A	1.07(0.91, 1.27)	0.416	0.879	T	A	1.02(0.94, 1.10)	0.696	>0.999
rs284794	*ADH7*	T	A	1.13(0.84, 1.51)	0.417	0.879	A	T	0.94(0.80, 1.09)	0.403	>0.999
rs3129200	*RXRB*	C	T	0.90(0.70, 1.16)	0.417	0.879	G	A	0.95(0.84, 1.06)	0.331	>0.999
rs4681028	*RARB*	T	G	1.08(0.89, 1.32)	0.427	0.880	T	G	1.08(0.98, 1.19)	0.116	>0.999
rs6775425	*RARB*	C	T	1.08(0.90, 1.30)	0.428	0.880	T	C	0.97(0.89, 1.06)	0.514	>0.999
rs1286657	*RARB*	G	C	1.07(0.90, 1.28)	0.430	0.880	G	C	0.98(0.90, 1.07)	0.689	>0.999
rs10489745	*RXRG*	C	T	0.90(0.68, 1.18)	0.430	0.880	C	T	1.04(0.90, 1.19)	0.613	>0.999

RR: Risk Ratio; **CI**: Confidence Interval; **OR**: Odds Ratio; --: Unavailable in replication study

SNP	Gene	NENA					CHOP				
		Minor Allele	Major Allele	RR (95% CI)	P-value	FDR Q-value	Minor Allele	Major Allele	OR (95% CI)	P-value	FDR Q-value
rs4889293	*BCMO1*	G	C	1.07(0.90, 1.26)	0.434	0.880	G	C	1.01(0.93, 1.09)	0.899	>0.999
rs517456	*RXRG*	C	G	0.92(0.74, 1.14)	0.437	0.880	C	G	1.03(0.92, 1.15)	0.613	>0.999
rs8031689	*CRABP1*	T	C	0.93(0.78, 1.12)	0.442	0.880	T	C	0.93(0.86, 1.01)	0.101	>0.999
rs11214106	*BCO2*	C	T	0.90(0.70, 1.17)	0.442	0.880	C	T	0.97(0.86, 1.09)	0.613	>0.999
rs12915846	*STRA6*	A	G	0.93(0.77, 1.12)	0.442	0.880	A	G	0.94(0.86, 1.02)	0.156	>0.999
rs361788	*ISX*	G	A	0.94(0.80, 1.11)	0.443	0.880	T	C	0.95(0.88, 1.03)	0.203	>0.999
rs7094671	*RBP4*	A	G	1.08(0.89, 1.30)	0.445	0.880	A	G	0.99(0.91, 1.09)	0.895	>0.999
rs1154470	*ADH7*	A	G	0.93(0.78, 1.12)	0.448	0.880	A	G	1.04(0.96, 1.13)	0.362	>0.999
rs1303629	*RARB*	G	T	0.93(0.77, 1.13)	0.449	0.880	G	T	1.01(0.92, 1.11)	0.892	>0.999
rs3814160	*RBP3*	T	C	1.10(0.86, 1.42)	0.449	0.880	T	C	0.92(0.81, 1.03)	0.149	>0.999
rs4384231	*CRABP2*	T	C	0.93(0.78, 1.12)	0.451	0.880	T	C	1.09(1.00, 1.18)	0.043	>0.999
rs1483856	*RARB*	C	A	1.11(0.85, 1.43)	0.454	0.880	T	G	0.99(0.88, 1.12)	0.9	>0.999
rs1547387	*RXRB*	C	G	0.91(0.70, 1.17)	0.454	0.880	G	C	0.95(0.84, 1.08)	0.445	>0.999
rs17583753	*ADH1A*	A	G	1.10(0.86, 1.41)	0.456	0.880	A	G	0.99(0.88, 1.11)	0.87	>0.999
rs918776	*BCMO1*	T	C	0.94(0.80, 1.11)	0.457	0.880	C	T	1.00(0.92, 1.08)	0.912	>0.999
rs941022	*RDH5*	G	T	0.94(0.79, 1.11)	0.459	0.881	C	A	0.90(0.83, 0.97)	0.009	>0.999
rs7629478	*RARB*	G	T	0.93(0.77, 1.12)	0.462	0.882	G	T	0.93(0.84, 1.03)	0.177	>0.999
rs7289450	*ISX*	C	G	1.07(0.89, 1.29)	0.467	0.884	C	G	1.02(0.93, 1.11)	0.696	>0.999
rs190910	*RBP1*	A	T	1.06(0.90, 1.26)	0.468	0.884	T	A	0.96(0.89, 1.04)	0.369	>0.999
rs17016584	*RARB*	G	C	1.12(0.82, 1.53)	0.471	0.884	G	C	0.89(0.77, 1.02)	0.099	>0.999
rs3758538	*RBP4*	C	A	1.08(0.87, 1.35)	0.472	0.884	G	T	0.96(0.86, 1.07)	0.474	>0.999
rs3768647	*CYP26B1*	C	G	1.09(0.87, 1.36)	0.473	0.884	C	G	0.95(0.85, 1.06)	0.353	>0.999
rs12420140	*BCO2*	A	G	1.07(0.89, 1.28)	0.479	0.884	A	G	1.02(0.93, 1.11)	0.701	>0.999
rs4492611	*CRABP2*	A	G	1.06(0.90, 1.25)	0.479	0.884	--	--	--	--	--
rs7182884	*ALDH1A3*	C	A	1.06(0.90, 1.27)	0.479	0.884	C	A	0.95(0.87, 1.03)	0.186	>0.999
rs1154477	*ADH7*	T	C	0.94(0.79, 1.12)	0.482	0.885	A	G	1.04(0.96, 1.12)	0.376	>0.999
rs11185662	*RXRA*	C	T	0.93(0.77, 1.13)	0.487	0.890	C	T	1.00(0.91, 1.10)	0.943	>0.999
rs7613553	*RARB*	A	C	0.94(0.79, 1.12)	0.489	0.890	A	C	0.94(0.86, 1.01)	0.097	>0.999
rs1902716	*RBP3*	C	T	0.93(0.76, 1.14)	0.491	0.890	A	G	1.01(0.91, 1.11)	0.869	>0.999
rs7845956	*RDH10*	A	G	0.88(0.60, 1.29)	0.496	0.895	G	A	0.98(0.83, 1.16)	0.816	>0.999
rs749759	*RXRA*	A	G	1.07(0.88, 1.30)	0.499	0.896	--	--	--	--	--
rs7606254	*CYP26B1*	T	C	0.93(0.74, 1.16)	0.507	0.902	T	C	0.95(0.85, 1.06)	0.377	>0.999
rs12723379	*RXRG*	G	A	1.06(0.90, 1.25)	0.511	0.902	G	A	0.99(0.92, 1.08)	0.898	>0.999
rs975020	*BCO2*	A	G	0.93(0.73, 1.17)	0.514	0.902	A	G	0.97(0.87, 1.09)	0.637	>0.999
rs1500372	*LRAT*	A	G	1.09(0.83, 1.43)	0.523	0.902	A	G	0.99(0.86, 1.14)	0.867	>0.999

RR: Risk Ratio; **CI**: Confidence Interval; **OR**: Odds Ratio; --: Unavailable in replication study

SNP	Gene	NENA					CHOP				
		Minor Allele	Major Allele	RR (95% CI)	P-value	FDR Q-value	Minor Allele	Major Allele	OR (95% CI)	P-value	FDR Q-value
rs11170481	*RARG*	A	G	0.91(0.67, 1.23)	0.524	0.902	--	--	--	--	--
rs707718	*CYP26B1*	A	C	0.93(0.76, 1.15)	0.524	0.902	T	G	0.99(0.90, 1.10)	0.876	>0.999
rs875444	*RXRA*	G	A	1.06(0.89, 1.25)	0.526	0.902	A	G	1.03(0.94, 1.13)	0.488	>0.999
rs6989495	*RDH10*	T	G	1.06(0.89, 1.25)	0.531	0.902	T	G	1.04(0.96, 1.13)	0.368	>0.999
rs12578814	*RDH5*	A	G	0.94(0.77, 1.14)	0.535	0.902	--	--	--	--	--
rs10736370	*RBP3*	C	T	0.95(0.80, 1.12)	0.535	0.902	T	C	0.98(0.90, 1.06)	0.592	>0.999
rs3010493	*PNLIP*	C	T	1.10(0.82, 1.47)	0.535	0.902	T	C	0.81(0.70, 0.93)	0.003	>0.999
rs6537944	*RXRA*	C	T	1.10(0.82, 1.48)	0.536	0.902	--	--	--	--	--
rs11187536	*RBP4*	T	G	1.06(0.88, 1.29)	0.539	0.902	T	G	1.01(0.92, 1.10)	0.895	>0.999
rs5999690	*ISX*	C	T	0.94(0.76, 1.16)	0.539	0.902	C	T	1.03(0.93, 1.14)	0.611	>0.999
rs4393871	*RARB*	T	C	0.95(0.80, 1.13)	0.539	0.902	C	T	1.01(0.93, 1.09)	0.866	>0.999
rs7768278	*ALDH8A1*	C	T	1.06(0.89, 1.25)	0.541	0.902	C	T	1.00(0.92, 1.08)	0.943	>0.999
rs34571439	*RBP4*	C	A	1.07(0.87, 1.32)	0.541	0.902	C	A	1.04(0.94, 1.15)	0.483	>0.999
rs284789	*ADH7*	C	T	0.95(0.79, 1.13)	0.542	0.902	G	A	1.03(0.94, 1.12)	0.528	>0.999
rs13314209	*RARB*	A	G	0.91(0.67, 1.24)	0.548	0.902	A	G	0.99(0.85, 1.15)	0.859	>0.999
rs283694	*RXRG*	T	C	1.05(0.89, 1.25)	0.553	0.902	T	C	1.06(0.97, 1.15)	0.195	>0.999
rs1554753	*RARG*	G	A	0.94(0.77, 1.15)	0.553	0.902	G	A	1.01(0.92, 1.12)	0.793	>0.999
rs10048138	*BCMO1*	A	G	1.07(0.86, 1.34)	0.555	0.902	G	A	1.10(0.98, 1.24)	0.092	>0.999
rs1286764	*RARB*	A	T	1.05(0.89, 1.25)	0.561	0.902	T	A	1.00(0.92, 1.08)	0.994	>0.999
rs13099641	*RARB*	A	T	1.08(0.84, 1.38)	0.561	0.902	A	T	0.94(0.84, 1.06)	0.313	>0.999
rs1286646	*RARB*	G	A	0.92(0.70, 1.21)	0.562	0.902	A	G	0.94(0.83, 1.07)	0.341	>0.999
rs1286740	*RARB*	G	C	1.05(0.89, 1.25)	0.562	0.902	C	G	1.03(0.95, 1.12)	0.452	>0.999
rs7039190	*RXRA*	C	A	0.88(0.58, 1.34)	0.562	0.902	C	A	0.99(0.82, 1.20)	0.938	>0.999
rs8187910	*ALDH1A1*	G	A	0.92(0.70, 1.21)	0.562	0.902	C	T	1.00(0.87, 1.14)	0.982	>0.999
rs3138140	*RDH5*	A	G	0.93(0.71, 1.21)	0.565	0.902	--	--	--	--	--
rs17016781	*RARB*	G	A	1.06(0.86, 1.32)	0.571	0.902	G	A	1.02(0.92, 1.13)	0.663	>0.999
rs3010496	*PNLIP*	A	G	1.06(0.86, 1.32)	0.576	0.902	G	A	0.90(0.81, 1.00)	0.053	>0.999
rs922939	*RARB*	G	T	0.95(0.80, 1.13)	0.577	0.902	A	C	1.07(0.98, 1.16)	0.111	>0.999
rs12907038	*ALDH1A2*	G	C	0.95(0.81, 1.13)	0.579	0.902	G	C	0.98(0.90, 1.06)	0.584	>0.999
rs2072915	*RXRB*	T	A	1.05(0.88, 1.25)	0.583	0.902	A	T	0.99(0.91, 1.07)	0.754	>0.999
rs6426914	*RXRG*	G	A	0.91(0.66, 1.26)	0.585	0.902	A	G	1.08(0.92, 1.28)	0.355	>0.999
rs2715554	*RARA*	C	T	0.93(0.73, 1.20)	0.586	0.902	G	A	0.98(0.87, 1.10)	0.7	>0.999
rs4681064	*RARB*	G	C	1.06(0.87, 1.29)	0.588	0.902	--	--	--	--	--
rs10786068	*CYP26A1*	C	G	1.05(0.88, 1.26)	0.590	0.902	G	C	0.97(0.89, 1.05)	0.417	>0.999
rs12442110	*CRABP1*	C	G	1.05(0.88, 1.26)	0.594	0.902	C	G	1.04(0.95, 1.13)	0.421	>0.999

RR: Risk Ratio; **CI**: Confidence Interval; **OR**: Odds Ratio; --: Unavailable in replication study

SNP	Gene	NENA					CHOP				
		Minor Allele	Major Allele	RR (95% CI)	P-value	FDR Q-value	Minor Allele	Major Allele	OR (95% CI)	P-value	FDR Q-value
rs3767339	*RXRG*	A	C	1.05(0.88, 1.24)	0.595	0.902	C	A	0.98(0.90, 1.07)	0.643	>0.999
rs17526721	*RARB*	G	A	1.09(0.79, 1.52)	0.597	0.902	G	A	1.08(0.93, 1.24)	0.327	>0.999
rs13070407	*RARB*	C	T	0.95(0.78, 1.15)	0.597	0.902	C	T	0.93(0.85, 1.01)	0.088	>0.999
rs4922517	*RBP3*	T	G	0.96(0.81, 1.13)	0.599	0.902	A	C	1.03(0.95, 1.11)	0.521	>0.999
rs4238328	*ALDH1A2*	A	G	1.06(0.86, 1.30)	0.600	0.902	A	G	0.99(0.89, 1.09)	0.773	>0.999
rs2194899	*RXRG*	A	G	0.96(0.81, 1.13)	0.605	0.902	G	A	0.97(0.89, 1.05)	0.458	>0.999
rs9937350	*BCMO1*	C	T	0.95(0.79, 1.15)	0.606	0.902	T	C	1.05(0.96, 1.15)	0.264	>0.999
rs351219	*STRA6*	C	T	1.05(0.88, 1.24)	0.612	0.902	C	T	1.02(0.94, 1.11)	0.575	>0.999
rs9494108	*ALDH8A1*	T	C	0.92(0.68, 1.26)	0.612	0.902	T	C	0.99(0.83, 1.17)	0.868	>0.999
rs12751264	*RXRG*	T	G	0.91(0.64, 1.31)	0.613	0.902	T	G	1.02(0.85, 1.23)	0.828	>0.999
rs6774124	*RARB*	G	C	0.96(0.80, 1.14)	0.616	0.902	G	C	1.04(0.95, 1.13)	0.425	>0.999
rs10203870	*CYP26B1*	A	C	0.94(0.75, 1.19)	0.618	0.902	A	C	1.06(0.96, 1.18)	0.251	>0.999
rs2654848	*ADH7*	A	T	1.04(0.88, 1.24)	0.618	0.902	T	A	1.05(0.97, 1.14)	0.231	>0.999
rs283695	*RXRG*	A	G	1.04(0.89, 1.23)	0.620	0.902	A	G	1.05(0.97, 1.13)	0.246	>0.999
rs9622121	*ISX*	C	T	1.04(0.88, 1.24)	0.623	0.902	T	C	1.05(0.97, 1.14)	0.224	>0.999
rs736118	*STRA6*	T	C	0.94(0.71, 1.22)	0.623	0.902	T	C	1.05(0.92, 1.21)	0.466	>0.999
rs10212330	*RARB*	A	T	0.95(0.78, 1.16)	0.624	0.902	T	A	1.01(0.92, 1.11)	0.874	>0.999
rs5995056	*ISX*	G	C	0.96(0.80, 1.14)	0.624	0.902	C	G	1.03(0.95, 1.12)	0.424	>0.999
rs1800458	*TTR*	A	G	0.92(0.66, 1.28)	0.625	0.902	A	G	1.03(0.89, 1.19)	0.693	>0.999
rs3803651	*BCMO1*	G	A	1.05(0.87, 1.27)	0.627	0.902	G	A	1.00(0.91, 1.10)	0.963	>0.999
rs4147531	*ADH1A*	T	C	1.04(0.88, 1.24)	0.631	0.905	A	G	1.05(0.97, 1.14)	0.213	>0.999
rs17326524	*STRA6*	C	T	0.92(0.66, 1.29)	0.635	0.905	C	T	1.09(0.93, 1.27)	0.278	>0.999
rs13085878	*RARB*	T	C	0.95(0.78, 1.17)	0.638	0.905	T	C	0.98(0.88, 1.08)	0.664	>0.999
rs5744222	*BCO2*	A	C	1.05(0.87, 1.27)	0.638	0.905	T	G	1.05(0.95, 1.15)	0.332	>0.999
rs2855425	*RXRB*	C	T	0.96(0.79, 1.15)	0.642	0.908	A	G	1.01(0.93, 1.10)	0.788	>0.999
rs3764478	*TTR*	A	C	1.06(0.81, 1.39)	0.650	0.917	T	G	1.04(0.92, 1.19)	0.513	>0.999
rs11089728	*ISX*	T	C	1.04(0.88, 1.24)	0.654	0.918	T	C	1.03(0.95, 1.11)	0.532	>0.999
rs7324	*CEL*	A	G	0.96(0.80, 1.15)	0.661	0.918	T	C	1.00(0.92, 1.09)	0.967	>0.999
rs6495089	*STRA6*	C	T	1.04(0.88, 1.23)	0.663	0.918	T	C	1.00(0.92, 1.08)	0.945	>0.999
rs1367038	*BCO2*	C	A	1.04(0.87, 1.25)	0.665	0.918	T	G	0.97(0.89, 1.06)	0.503	>0.999
rs17529377	*ADH7*	C	T	0.95(0.74, 1.21)	0.666	0.918	C	T	0.98(0.87, 1.11)	0.774	>0.999
rs348464	*ALDH1A1*	T	A	1.04(0.86, 1.27)	0.667	0.918	A	T	0.91(0.83, 1.00)	0.049	>0.999
rs1286766	*RARB*	T	A	0.96(0.81, 1.14)	0.668	0.918	T	A	1.03(0.95, 1.12)	0.444	>0.999
rs1286772	*RARB*	C	G	0.96(0.81, 1.15)	0.669	0.918	G	C	1.03(0.95, 1.11)	0.539	>0.999
rs941138	*RARG*	C	T	0.94(0.69, 1.27)	0.672	0.918	--	--	--	--	--

RR: Risk Ratio; **CI**: Confidence Interval; **OR**: Odds Ratio; --: Unavailable in replication study

SNP	Gene	NENA					CHOP				
		Minor Allele	Major Allele	RR (95% CI)	P-value	FDR Q-value	Minor Allele	Major Allele	OR (95% CI)	P-value	FDR Q-value
rs887844	*CYP26B1*	C	T	0.96(0.81, 1.15)	0.673	0.918	--	--	--	--	--
rs1997353	*RARB*	G	A	0.97(0.81, 1.14)	0.678	0.919	T	C	0.99(0.91, 1.07)	0.805	>0.999
rs8187889	*ALDH1A1*	C	T	0.93(0.65, 1.33)	0.679	0.919	G	A	1.03(0.87, 1.23)	0.731	>0.999
rs1286769	*RARB*	T	C	1.04(0.88, 1.23)	0.680	0.919	A	G	1.02(0.94, 1.10)	0.658	>0.999
rs9937486	*BCMO1*	G	C	1.07(0.76, 1.51)	0.683	0.919	G	C	1.08(0.90, 1.30)	0.415	>0.999
rs2192332	*CYP26B1*	G	T	1.04(0.86, 1.26)	0.686	0.919	C	A	0.98(0.90, 1.07)	0.662	>0.999
rs157865	*RXRG*	A	C	0.97(0.82, 1.14)	0.691	0.919	A	C	1.00(0.92, 1.08)	1	>0.999
rs3132301	*RXRA*	T	C	1.04(0.85, 1.29)	0.694	0.919	G	A	0.99(0.90, 1.10)	0.907	>0.999
rs11187545	*RBP4*	G	A	1.06(0.78, 1.44)	0.695	0.919	G	A	0.96(0.83, 1.11)	0.595	>0.999
rs28709456	*CES1*	C	A	0.95(0.74, 1.22)	0.696	0.919	--	--	--	--	--
rs4646870	*ALDH8A1*	T	G	1.04(0.87, 1.23)	0.701	0.919	A	C	1.01(0.93, 1.10)	0.741	>0.999
rs6721368	*CYP26B1*	G	T	0.94(0.69, 1.29)	0.702	0.919	G	T	0.91(0.78, 1.07)	0.273	>0.999
rs362166	*ISX*	A	G	0.94(0.70, 1.28)	0.704	0.919	T	C	0.83(0.70, 0.98)	0.032	>0.999
rs7621140	*RARB*	C	T	1.05(0.82, 1.33)	0.705	0.919	C	T	0.96(0.85, 1.08)	0.493	>0.999
rs360722	*BCO2*	T	C	0.95(0.74, 1.23)	0.705	0.919	G	A	1.02(0.90, 1.15)	0.729	>0.999
rs11187531	*RBP4*	C	T	1.06(0.79, 1.42)	0.707	0.919	C	T	0.96(0.84, 1.10)	0.604	>0.999
rs12169293	*ISX*	A	G	1.05(0.81, 1.38)	0.708	0.919	A	G	1.03(0.90, 1.17)	0.687	>0.999
rs7922067	*CYP26C1*	G	A	0.97(0.82, 1.15)	0.710	0.920	A	G	0.96(0.88, 1.04)	0.28	>0.999
rs6587052	*RBP3*	C	T	0.97(0.80, 1.16)	0.715	0.923	C	T	1.01(0.93, 1.11)	0.788	>0.999
rs10427677	*ISX*	C	A	1.04(0.84, 1.30)	0.718	0.923	C	A	1.06(0.95, 1.18)	0.313	>0.999
rs6778350	*RARB*	A	G	1.04(0.82, 1.32)	0.722	0.925	G	A	1.01(0.90, 1.12)	0.926	>0.999
rs16938613	*RDH10*	C	A	0.95(0.73, 1.24)	0.725	0.925	C	A	0.96(0.84, 1.09)	0.493	>0.999
rs17525900	*RARB*	C	T	0.96(0.74, 1.23)	0.726	0.925	C	T	1.03(0.91, 1.16)	0.663	>0.999
rs8187950	*ALDH1A1*	C	T	0.92(0.57, 1.49)	0.728	0.925	G	A	1.02(0.83, 1.25)	0.834	>0.999
rs7616467	*RARB*	T	C	1.03(0.87, 1.22)	0.736	0.933	--	--	--	--	--
rs4890109	*RARA*	T	G	0.93(0.60, 1.44)	0.738	0.933	T	G	0.92(0.75, 1.11)	0.379	>0.999
rs1154454	*ADH7*	C	T	0.96(0.77, 1.20)	0.742	0.934	G	A	1.06(0.95, 1.18)	0.282	>0.999
rs2073821	*CEL*	T	C	1.04(0.81, 1.34)	0.743	0.934	T	C	1.02(0.90, 1.16)	0.757	>0.999
rs17016566	*RARB*	G	C	0.95(0.70, 1.29)	0.746	0.935	G	C	1.00(0.86, 1.17)	0.956	>0.999
rs1799908	*RXRB*	T	A	0.97(0.83, 1.15)	0.749	0.935	A	T	1.02(0.95, 1.11)	0.545	>0.999
rs11103603	*RXRA*	C	T	0.97(0.82, 1.16)	0.751	0.935	--	--	--	--	--
rs1968481	*RARB*	G	A	0.95(0.68, 1.33)	0.767	0.935	G	A	1.04(0.89, 1.21)	0.659	>0.999
rs5750056	*ISX*	T	C	1.05(0.76, 1.45)	0.768	0.935	T	C	1.17(0.99, 1.39)	0.072	>0.999
rs156499	*LRAT*	C	A	0.97(0.80, 1.18)	0.772	0.935	G	T	0.98(0.89, 1.08)	0.658	>0.999
rs11858606	*ALDH1A2*	C	T	1.04(0.79, 1.38)	0.773	0.935	--	--	--	--	--

RR: Risk Ratio; **CI**: Confidence Interval; **OR**: Odds Ratio; --: Unavailable in replication study

SNP	Gene	NENA					CHOP				
		Minor Allele	Major Allele	RR (95% CI)	P-value	FDR Q-value	Minor Allele	Major Allele	OR (95% CI)	P-value	FDR Q-value
rs595958	*ALDH1A1*	A	G	1.03(0.86, 1.22)	0.774	0.935	T	C	0.95(0.87, 1.03)	0.204	>0.999
rs11214125	*BCO2*	T	C	1.04(0.78, 1.39)	0.776	0.935	T	C	1.06(0.92, 1.22)	0.388	>0.999
rs10082776	*RARG*	G	A	0.96(0.73, 1.27)	0.781	0.935	G	A	1.09(0.95, 1.26)	0.229	>0.999
rs12526336	*RXRB*	A	G	0.97(0.76, 1.23)	0.786	0.935	A	G	1.04(0.92, 1.18)	0.515	>0.999
rs4646548	*ALDH1A1*	C	T	1.04(0.78, 1.39)	0.787	0.935	G	A	1.10(0.93, 1.29)	0.257	>0.999
rs1583977	*ADH7*	T	A	0.97(0.75, 1.24)	0.789	0.935	A	T	1.07(0.94, 1.20)	0.296	>0.999
rs8027180	*CRABP1*	A	G	1.02(0.87, 1.21)	0.789	0.935	G	A	1.00(0.93, 1.09)	0.908	>0.999
rs11187529	*RBP4*	T	C	1.06(0.69, 1.63)	0.791	0.935	T	C	1.07(0.86, 1.33)	0.53	>0.999
rs11818333	*RBP3*	A	T	1.04(0.77, 1.42)	0.793	0.935	A	T	1.06(0.91, 1.24)	0.462	>0.999
rs17016408	*RARB*	C	G	1.03(0.81, 1.33)	0.794	0.935	C	G	1.03(0.91, 1.17)	0.64	>0.999
rs7637031	*RARB*	T	G	1.02(0.86, 1.21)	0.796	0.935	T	G	1.03(0.95, 1.12)	0.475	>0.999
rs11630924	*STRA6*	C	G	1.03(0.83, 1.27)	0.796	0.935	C	G	0.95(0.86, 1.05)	0.327	>0.999
rs4738315	*RDH10*	A	G	0.98(0.81, 1.18)	0.801	0.935	A	G	1.05(0.96, 1.15)	0.283	>0.999
rs1992005	*RARB*	T	C	1.04(0.77, 1.40)	0.803	0.935	A	G	1.06(0.91, 1.23)	0.45	>0.999
rs1888202	*ALDH1A1*	G	C	1.02(0.87, 1.20)	0.803	0.935	G	C	1.06(0.98, 1.16)	0.147	>0.999
rs925987	*CRABP1*	C	T	1.02(0.86, 1.21)	0.804	0.935	T	C	0.96(0.89, 1.05)	0.389	>0.999
rs6805350	*RARB*	G	T	1.04(0.75, 1.44)	0.804	0.935	G	T	1.14(0.97, 1.34)	0.117	>0.999
rs7139068	*RARG*	T	A	0.97(0.73, 1.28)	0.804	0.935	--	--	--	--	--
rs3138144	*RDH5*	G	C	0.98(0.83, 1.16)	0.806	0.935	--	--	--	--	--
rs1432603	*RARB*	C	T	0.98(0.80, 1.19)	0.808	0.935	T	C	1.01(0.92, 1.11)	0.895	>0.999
rs6805482	*RARB*	A	G	1.02(0.86, 1.21)	0.808	0.935	--	--	--	--	--
rs11214127	*BCO2*	A	G	0.98(0.81, 1.18)	0.808	0.935	A	G	0.99(0.91, 1.09)	0.871	>0.999
rs6835524	*ADH7*	T	C	0.97(0.76, 1.25)	0.810	0.935	C	T	0.95(0.84, 1.07)	0.389	>0.999
rs3803435	*ALDH1A3*	G	C	1.03(0.80, 1.32)	0.813	0.937	--	--	--	--	--
rs285482	*RXRG*	T	G	0.98(0.82, 1.17)	0.816	0.937	T	G	1.02(0.93, 1.11)	0.739	>0.999
rs11999628	*ALDH1A1*	T	G	0.96(0.66, 1.41)	0.833	0.954	T	G	0.99(0.83, 1.19)	0.942	>0.999
rs3899272	*RXRA*	T	A	1.04(0.74, 1.45)	0.836	0.954	T	A	0.99(0.84, 1.15)	0.873	>0.999
rs12635733	*RARB*	C	T	0.97(0.71, 1.33)	0.841	0.958	C	T	1.05(0.90, 1.22)	0.522	>0.999
rs13325144	*RBP2*	A	G	1.03(0.79, 1.33)	0.844	0.959	A	G	1.00(0.89, 1.12)	0.974	>0.999
rs351224	*STRA6*	T	A	0.98(0.84, 1.16)	0.846	0.959	A	T	1.05(0.97, 1.13)	0.24	>0.999
rs3757971	*DGAT1*	G	A	0.98(0.83, 1.17)	0.857	0.964	C	T	0.98(0.90, 1.07)	0.686	>0.999
rs11645428	*BCMO1*	A	G	0.98(0.83, 1.17)	0.857	0.964	A	G	1.03(0.95, 1.12)	0.506	>0.999
rs6550981	*RARB*	G	C	1.02(0.86, 1.19)	0.858	0.964	--	--	--	--	--
rs12753930	*CRABP2*	A	G	0.99(0.83, 1.17)	0.860	0.965	G	A	1.08(0.99, 1.17)	0.079	>0.999
rs380518	*RXRG*	C	T	1.02(0.82, 1.27)	0.863	0.965	T	C	1.00(0.90, 1.12)	0.944	>0.999

RR: Risk Ratio; **CI**: Confidence Interval; **OR**: Odds Ratio; --: Unavailable in replication study

SNP	Gene	NENA					CHOP				
		Minor Allele	Major Allele	RR (95% CI)	P-value	FDR Q-value	Minor Allele	Major Allele	OR (95% CI)	P-value	FDR Q-value
rs1286665	*RARB*	T	C	0.99(0.83, 1.18)	0.866	0.966	T	C	0.96(0.88, 1.05)	0.382	>0.999
rs746332	*RXRG*	A	C	1.02(0.81, 1.28)	0.870	0.968	A	C	1.00(0.89, 1.12)	0.973	>0.999
rs12249434	*PNLIP*	T	C	0.98(0.73, 1.30)	0.872	0.968	T	C	1.01(0.88, 1.15)	0.938	>0.999
rs2012147	*ALDH1A2*	T	C	0.97(0.68, 1.39)	0.878	0.968	G	A	0.82(0.68, 0.99)	0.038	>0.999
rs4349972	*RDH10*	T	C	1.01(0.85, 1.20)	0.878	0.968	C	T	1.07(0.99, 1.16)	0.091	>0.999
rs7536331	*RXRG*	G	A	1.01(0.86, 1.19)	0.881	0.968	A	G	0.98(0.91, 1.07)	0.683	>0.999
rs11715516	*RARB*	G	C	0.98(0.79, 1.23)	0.883	0.968	C	G	0.97(0.88, 1.08)	0.576	>0.999
rs4935984	*BCO2*	A	G	1.01(0.85, 1.21)	0.884	0.968	A	G	1.00(0.92, 1.09)	0.987	>0.999
rs1626875	*RARB*	T	C	0.99(0.80, 1.21)	0.891	0.969	A	G	0.95(0.86, 1.05)	0.312	>0.999
rs4887066	*STRA6*	T	C	0.98(0.76, 1.27)	0.892	0.969	C	T	0.94(0.82, 1.07)	0.325	>0.999
rs12903202	*ALDH1A2*	G	A	0.98(0.72, 1.33)	0.893	0.969	G	A	0.94(0.82, 1.08)	0.406	>0.999
rs213210	*RXRB*	C	T	1.02(0.76, 1.37)	0.894	0.969	--	--	--	--	--
rs11642457	*BCMO1*	G	A	1.01(0.85, 1.20)	0.902	0.973	A	G	1.02(0.94, 1.10)	0.653	>0.999
rs2272301	*RARG*	G	C	1.02(0.79, 1.31)	0.904	0.973	--	--	--	--	--
rs295492	*RBP1*	T	C	0.99(0.83, 1.18)	0.906	0.973	C	T	0.97(0.89, 1.05)	0.473	>0.999
rs6564851	*BCMO1*	T	G	1.01(0.86, 1.19)	0.907	0.973	G	T	1.03(0.95, 1.11)	0.535	>0.999
rs12759184	*CRABP2*	T	C	1.01(0.85, 1.21)	0.914	0.976	T	C	0.93(0.86, 1.01)	0.097	>0.999
rs4607073	*RARB*	G	T	0.99(0.84, 1.17)	0.915	0.976	T	G	1.01(0.93, 1.09)	0.839	>0.999
rs2041666	*CYP26B1*	A	C	0.99(0.79, 1.23)	0.917	0.976	T	G	0.99(0.89, 1.10)	0.912	>0.999
rs8187884	*ALDH1A1*	T	G	0.98(0.71, 1.37)	0.919	0.976	A	C	1.01(0.88, 1.17)	0.85	>0.999
rs348483	*ALDH1A1*	C	T	0.99(0.79, 1.25)	0.926	0.982	C	T	0.90(0.81, 1.00)	0.054	>0.999
rs1286754	*RARB*	T	C	0.99(0.84, 1.18)	0.929	0.982	T	C	1.02(0.94, 1.10)	0.693	>0.999
rs6569976	*ALDH8A1*	C	A	1.01(0.85, 1.19)	0.935	0.982	A	C	1.02(0.94, 1.11)	0.633	>0.999
rs11143419	*ALDH1A1*	C	G	1.01(0.86, 1.19)	0.936	0.982	--	--	--	--	--
rs12929595	*BCMO1*	A	G	0.99(0.82, 1.21)	0.936	0.982	G	A	1.02(0.93, 1.12)	0.66	>0.999
rs12932003	*BCMO1*	G	A	1.01(0.85, 1.19)	0.940	0.983	G	A	0.95(0.87, 1.04)	0.233	>0.999
rs7620529	*RARB*	A	C	1.01(0.85, 1.20)	0.941	0.983	C	A	1.03(0.95, 1.12)	0.413	>0.999
rs3762894	*ADH4*	C	T	0.99(0.80, 1.24)	0.950	0.987	C	T	1.00(0.90, 1.11)	0.99	>0.999
rs3813573	*CRABP1*	A	G	0.99(0.80, 1.23)	0.950	0.987	T	C	0.99(0.90, 1.09)	0.834	>0.999
rs1286641	*RARB*	T	A	1.00(0.85, 1.19)	0.960	0.988	T	A	0.95(0.88, 1.04)	0.259	>0.999
rs4418728	*CYP26A1*	T	G	1.00(0.84, 1.18)	0.964	0.988	T	G	1.03(0.96, 1.12)	0.417	>0.999
rs11089722	*ISX*	G	C	1.00(0.83, 1.20)	0.967	0.988	G	C	1.01(0.93, 1.10)	0.744	>0.999
rs34745537	*RARG*	A	G	1.00(0.85, 1.18)	0.972	0.988	--	--	--	--	--
rs4646615	*ALDH1A2*	T	G	1.00(0.84, 1.19)	0.975	0.988	A	C	1.02(0.93, 1.11)	0.679	>0.999
rs10518951	*ALDH1A2*	A	C	1.01(0.72, 1.40)	0.976	0.988	A	C	0.95(0.81, 1.10)	0.47	>0.999

RR: Risk Ratio; **CI**: Confidence Interval; **OR**: Odds Ratio; --: Unavailable in replication study

SNP	Gene	NENA					CHOP				
		Minor Allele	Major Allele	RR (95% CI)	P-value	FDR Q-value	Minor Allele	Major Allele	OR (95% CI)	P-value	FDR Q-value
rs351229	*STRA6*	C	A	1.00(0.78, 1.30)	0.976	0.988	T	G	0.98(0.86, 1.12)	0.775	>0.999
rs3741434	*RARG*	G	A	1.00(0.78, 1.28)	0.976	0.988	C	T	1.01(0.90, 1.13)	0.82	>0.999
rs11635868	*STRA6*	T	C	1.00(0.75, 1.33)	0.979	0.988	T	C	0.96(0.83, 1.10)	0.531	>0.999
rs348463	*ALDH1A1*	C	T	1.00(0.83, 1.20)	0.980	0.988	C	T	0.95(0.87, 1.04)	0.257	>0.999
rs6564864	*BCMO1*	T	G	1.00(0.85, 1.18)	0.980	0.988	T	G	1.04(0.96, 1.12)	0.364	>0.999
rs2070706	*RBP3*	A	G	1.00(0.84, 1.19)	0.984	0.988	C	T	1.06(0.97, 1.15)	0.188	>0.999
rs5750044	*ISX*	T	G	1.00(0.72, 1.40)	0.985	0.988	T	G	1.13(0.95, 1.33)	0.159	>0.999
rs7291929	*ISX*	A	G	1.00(0.73, 1.38)	0.987	0.988	A	G	0.99(0.85, 1.16)	0.933	>0.999
rs1435705	*RARB*	A	G	1.00(0.76, 1.32)	0.987	0.988	A	G	1.04(0.91, 1.19)	0.542	>0.999
rs17778240	*ISX*	T	A	1.00(0.85, 1.19)	0.988	0.988	T	A	1.02(0.94, 1.10)	0.657	>0.999

RR: Risk Ratio; **CI**: Confidence Interval; **OR**: Odds Ratio; --: Unavailable in replication study

APPENDIX 2. RESULTS FROM MATERNAL VITAMIN A-RELATED SNPS

SNP	Gene	Minor Allele	Major Allele	RR (95% CI)	P-value	Q-value
rs4842196	*RXRA*	C	A	0.90(0.76, 1.06)	0.189	0.820
rs1229977	*ADH1A*	T	C	0.88(0.73, 1.06)	0.185	0.820
rs1045570	*RXRA*	T	G	1.01(0.81, 1.26)	0.930	0.984
rs1007971	*RXRA*	G	C	0.98(0.83, 1.16)	0.804	0.984
rs7139068	*RARG*	T	A	0.90(0.74, 1.09)	0.268	0.876
rs904092	*ADH1A*	A	G	0.76(0.59, 0.99)	0.043	0.696
rs3118523	*RXRA*	G	A	0.78(0.66, 0.93)	0.005	0.274
rs7169439	*ALDH1A2*	A	G	0.94(0.76, 1.18)	0.616	0.927
rs1465057	*RARG*	C	T	0.89(0.74, 1.08)	0.250	0.876
rs748964	*RXRA*	C	G	0.97(0.78, 1.22)	0.811	0.984
rs362166	*ISX*	A	G	0.96(0.77, 1.19)	0.695	0.947
rs6569976	*ALDH8A1*	C	A	1.08(0.80, 1.45)	0.618	0.927
rs2899240	*ISX*	G	A	0.70(0.49, 0.99)	0.044	0.696
rs10032099	*ADH4*	G	A	1.12(0.94, 1.32)	0.206	0.854
rs10009145	*ADH4*	A	G	0.85(0.69, 1.05)	0.137	0.784
rs4699710	*ADH4*	C	T	1.06(0.89, 1.25)	0.539	0.911
rs28709456	*CES1*	C	A	0.98(0.83, 1.16)	0.856	0.984
rs6778350	*RARB*	A	G	1.07(0.90, 1.26)	0.462	0.904
rs11917304	*RARB*	C	T	0.82(0.62, 1.07)	0.148	0.784
rs283695	*RXRG*	A	G	0.89(0.75, 1.06)	0.192	0.820
rs7670060	*ADH4*	T	G	1.00(0.84, 1.19)	0.971	0.984
rs12526336	*RXRB*	A	G	1.09(0.92, 1.27)	0.316	0.876
rs5995056	*ISX*	G	C	0.99(0.83, 1.18)	0.904	0.984
rs380518	*RXRG*	C	T	1.10(0.92, 1.31)	0.312	0.876
rs3758495	*RBP3*	A	G	0.90(0.76, 1.07)	0.237	0.864
rs283694	*RXRG*	T	C	0.85(0.72, 1.00)	0.054	0.703
rs11170481	*RARG*	A	G	0.96(0.82, 1.13)	0.615	0.927
rs12753930	*CRABP2*	A	G	0.75(0.52, 1.08)	0.120	0.784
rs9373116	*ALDH8A1*	C	G	0.90(0.66, 1.22)	0.493	0.904
rs6799734	*RARB*	C	G	0.92(0.76, 1.13)	0.443	0.904
rs1538648	*CYP26C1*	C	T	1.04(0.81, 1.33)	0.764	0.962
rs11926758	*RARB*	T	G	0.90(0.61, 1.34)	0.618	0.927
rs1554753	*RARG*	G	A	1.11(0.84, 1.47)	0.453	0.904
rs2364120	*RARB*	G	A	1.06(0.88, 1.27)	0.561	0.919
rs11858606	*ALDH1A2*	C	T	1.03(0.75, 1.42)	0.852	0.984
rs5755550	*ISX*	C	T	1.03(0.78, 1.36)	0.856	0.984
rs4266713	*ALDH1A1*	A	T	0.72(0.56, 0.94)	0.014	0.447
rs2120200	*RARA*	G	A	0.79(0.61, 1.03)	0.087	0.778
rs6550981	*RARB*	G	C	0.76(0.57, 1.03)	0.075	0.778
rs3817776	*ALDH8A1*	C	T	0.76(0.63, 0.91)	0.004	0.274
rs941138	*RARG*	C	T	0.83(0.64, 1.08)	0.170	0.807

RR: Risk ratio; **CI**: Confidence interval

SNP	Gene	Minor Allele	Major Allele	RR (95% CI)	P-value	Q-value
rs10885982	*PNLIP*	A	G	1.20(0.95, 1.51)	0.129	0.784
rs2116703	*RARB*	A	G	0.98(0.82, 1.17)	0.849	0.984
rs285482	*RXRG*	T	G	1.00(0.84, 1.20)	0.973	0.984
rs6805350	*RARB*	G	T	1.00(0.84, 1.19)	1.000	1.000
rs1286658	*RARB*	T	C	0.91(0.73, 1.13)	0.407	0.904
rs12730752	*CRABP2*	T	C	1.02(0.85, 1.21)	0.858	0.984
rs4681064	*RARB*	G	C	1.12(0.91, 1.38)	0.287	0.876
rs17526721	*RARB*	G	A	1.02(0.82, 1.28)	0.832	0.984
rs5750056	*ISX*	T	C	0.94(0.80, 1.12)	0.497	0.904
rs1286740	*RARB*	G	C	0.96(0.80, 1.15)	0.671	0.947
rs1805343	*RXRA*	G	A	1.00(0.84, 1.18)	0.976	0.985
rs10082776	*RARG*	G	A	1.03(0.87, 1.23)	0.727	0.947
rs3810619	*ISX*	T	C	1.13(0.91, 1.39)	0.273	0.876
rs1902716	*RBP3*	C	T	1.09(0.89, 1.34)	0.386	0.904
rs6767543	*RARB*	G	A	0.82(0.62, 1.09)	0.173	0.807
rs11264527	*CRABP2*	C	T	0.87(0.75, 1.03)	0.099	0.778
rs5750044	*ISX*	T	G	1.00(0.84, 1.20)	0.957	0.984
rs12648206	*ADH7*	G	A	1.10(0.93, 1.29)	0.255	0.876
rs1800759	*ADH4*	A	C	0.94(0.76, 1.17)	0.603	0.927
rs17778240	*ISX*	T	A	1.21(1.00, 1.46)	0.056	0.703
rs6495089	*STRA6*	C	T	0.80(0.60, 1.06)	0.120	0.784
rs4492611	*CRABP2*	A	G	1.13(0.94, 1.35)	0.191	0.820
rs4738315	*RDH10*	A	G	0.83(0.62, 1.11)	0.213	0.854
rs2073821	*CEL*	T	C	0.82(0.67, 0.99)	0.041	0.696
rs9622121	*ISX*	C	T	0.91(0.74, 1.11)	0.350	0.899
rs6669441	*RXRG*	A	G	1.23(0.96, 1.57)	0.108	0.778
rs10918179	*RXRG*	A	C	1.02(0.75, 1.39)	0.911	0.984
rs4646548	*ALDH1A1*	C	T	0.75(0.51, 1.10)	0.137	0.784
rs4240705	*RXRA*	G	A	0.99(0.75, 1.31)	0.943	0.984
rs17016570	*RARB*	G	A	0.80(0.60, 1.07)	0.128	0.784
rs12573026	*RBP4*	C	T	1.14(0.96, 1.37)	0.145	0.784
rs1864907	*RARB*	G	A	0.96(0.81, 1.14)	0.631	0.930
rs1286750	*RARB*	C	A	1.07(0.87, 1.31)	0.501	0.904
rs2070706	*RBP3*	A	G	1.06(0.88, 1.28)	0.537	0.911
rs2194899	*RXRG*	A	G	0.61(0.47, 0.79)	0.000	0.076
rs3010493	*PNLIP*	C	T	1.07(0.89, 1.27)	0.474	0.904
rs17583753	*ADH1A*	A	G	0.94(0.79, 1.11)	0.445	0.904
rs3899272	*RXRA*	T	A	1.28(0.96, 1.71)	0.096	0.778
rs1500372	*LRAT*	A	G	1.03(0.88, 1.22)	0.699	0.947
rs10910	*STRA6*	G	A	1.03(0.81, 1.32)	0.800	0.984
rs17108978	*RBP4*	A	G	0.93(0.73, 1.19)	0.568	0.920
rs11214139	*BCO2*	G	A	0.94(0.77, 1.14)	0.538	0.911
rs1153592	*RARB*	A	T	0.85(0.62, 1.15)	0.292	0.876

RR: Risk ratio; **CI**: Confidence interval

SNP	Gene	Minor Allele	Major Allele	RR (95% CI)	P-value	Q-value
rs6795340	*RARB*	A	G	0.98(0.80, 1.19)	0.842	0.984
rs482284	*RARA*	A	G	1.04(0.88, 1.22)	0.629	0.930
rs1286664	*RARB*	T	C	1.01(0.85, 1.19)	0.947	0.984
rs1730221	*RARB*	G	C	1.06(0.87, 1.28)	0.573	0.921
rs3803651	*BCMO1*	G	A	0.85(0.61, 1.20)	0.363	0.904
rs6909923	*ALDH8A1*	G	A	0.90(0.75, 1.07)	0.230	0.864
rs11865869	*BCMO1*	G	A	1.03(0.86, 1.24)	0.729	0.947
rs752739	*RXRG*	T	C	1.04(0.88, 1.23)	0.649	0.946
rs3767339	*RXRG*	A	C	1.12(0.87, 1.44)	0.386	0.904
rs156499	*LRAT*	C	A	1.02(0.86, 1.20)	0.840	0.984
rs9879736	*RBP1*	T	C	1.04(0.87, 1.24)	0.692	0.947
rs3762894	*ADH4*	C	T	1.07(0.90, 1.27)	0.434	0.904
rs11580324	*CRABP2*	C	G	0.94(0.72, 1.23)	0.677	0.947
rs348458	*ALDH1A1*	A	G	0.93(0.76, 1.14)	0.491	0.904
rs11187549	*RBP4*	G	A	1.07(0.89, 1.29)	0.451	0.904
rs3818730	*RXRA*	A	G	1.13(0.91, 1.39)	0.275	0.876
rs4646669	*ALDH1A3*	T	C	1.11(0.91, 1.34)	0.300	0.876
rs11089722	*ISX*	G	C	1.16(0.98, 1.38)	0.088	0.778
rs8187945	*ALDH1A1*	T	C	1.01(0.85, 1.20)	0.951	0.984
rs2715553	*RARA*	C	T	1.00(0.85, 1.18)	0.963	0.984
rs13120304	*ADH1A*	A	T	1.12(0.95, 1.33)	0.164	0.807
rs1153606	*RARB*	G	A	0.82(0.70, 0.97)	0.022	0.609
rs2156731	*ADH4*	A	G	1.16(0.99, 1.36)	0.074	0.778
rs12906432	*ALDH1A3*	T	G	0.94(0.79, 1.11)	0.469	0.904
rs6564851	*BCMO1*	T	G	1.00(0.79, 1.26)	0.996	0.998
rs3803435	*ALDH1A3*	G	C	1.05(0.77, 1.41)	0.771	0.963
rs5750041	*ISX*	T	C	1.04(0.87, 1.25)	0.669	0.947
rs4238328	*ALDH1A2*	A	G	1.06(0.90, 1.25)	0.509	0.904
rs1286650	*RARB*	A	T	0.85(0.70, 1.04)	0.108	0.778
rs749759	*RXRA*	A	G	1.15(0.94, 1.41)	0.173	0.807
rs283697	*RXRG*	A	C	0.85(0.72, 1.00)	0.051	0.703
rs157861	*RXRG*	G	C	1.08(0.91, 1.28)	0.399	0.904
rs348483	*ALDH1A1*	C	T	0.93(0.77, 1.13)	0.477	0.904
rs12907038	*ALDH1A2*	G	C	1.22(1.01, 1.47)	0.038	0.696
rs1229966	*ADH1A*	C	T	0.85(0.69, 1.05)	0.143	0.784
rs1154460	*ADH7*	A	G	1.13(0.88, 1.45)	0.340	0.891
rs8187884	*ALDH1A1*	T	G	0.94(0.79, 1.12)	0.520	0.911
rs11264518	*CRABP2*	T	C	1.13(0.81, 1.57)	0.469	0.904
rs351224	*STRA6*	T	A	1.21(0.94, 1.56)	0.136	0.784
rs4646678	*ALDH1A3*	T	C	0.91(0.76, 1.09)	0.327	0.882
rs7922067	*CYP26C1*	G	A	1.09(0.92, 1.29)	0.315	0.876
rs4890109	*RARA*	T	G	0.99(0.85, 1.16)	0.935	0.984
rs361788	*ISX*	G	A	0.91(0.75, 1.10)	0.319	0.876

RR: Risk ratio; **CI**: Confidence interval

SNP	Gene	Minor Allele	Major Allele	RR (95% CI)	P-value	Q-value
rs1108197	*RBP4*	A	G	0.88(0.66, 1.17)	0.378	0.904
rs941022	*RDH5*	G	T	0.87(0.67, 1.13)	0.302	0.876
rs3813573	*CRABP1*	A	G	0.94(0.73, 1.22)	0.657	0.947
rs9937486	*BCMO1*	G	C	0.86(0.72, 1.02)	0.089	0.778
rs7663410	*ADH7*	C	A	0.87(0.67, 1.14)	0.316	0.876
rs6762247	*RARB*	T	C	0.93(0.74, 1.16)	0.509	0.904
rs8181419	*RBP4*	G	T	0.92(0.78, 1.09)	0.343	0.891
rs3773438	*RARB*	A	G	0.95(0.73, 1.23)	0.703	0.947
rs975020	*BCO2*	A	G	0.87(0.71, 1.08)	0.210	0.854
rs6771831	*RBP2*	A	G	1.02(0.85, 1.24)	0.819	0.984
rs4699720	*ADH4*	C	T	1.19(0.94, 1.51)	0.148	0.784
rs12512110	*ADH1A*	T	G	1.10(0.89, 1.36)	0.355	0.904
rs167187	*RBP1*	G	A	1.11(0.88, 1.40)	0.360	0.904
rs17016566	*RARB*	G	C	0.99(0.83, 1.17)	0.871	0.984
rs12420140	*BCO2*	A	G	0.87(0.68, 1.11)	0.262	0.876
rs7541159	*RXRG*	T	G	1.15(0.94, 1.41)	0.186	0.820
rs6803265	*RARB*	A	T	0.93(0.78, 1.11)	0.424	0.904
rs13314209	*RARB*	A	G	1.29(1.05, 1.58)	0.015	0.447
rs16844995	*RXRG*	C	T	1.17(0.90, 1.53)	0.250	0.876
rs6805482	*RARB*	A	G	1.13(0.87, 1.45)	0.364	0.904
rs3772879	*RBP2*	T	A	1.16(0.86, 1.57)	0.317	0.876
rs970902	*RXRB*	G	A	1.29(0.92, 1.80)	0.141	0.784
rs11089728	*ISX*	T	C	1.17(0.86, 1.59)	0.312	0.876
rs12751264	*RXRG*	T	G	1.11(0.88, 1.40)	0.388	0.904
rs12723379	*RXRG*	G	A	1.08(0.88, 1.32)	0.477	0.904
rs7536331	*RXRG*	G	A	1.09(0.90, 1.33)	0.383	0.904
rs11170466	*RARG*	A	G	1.03(0.84, 1.27)	0.764	0.962
rs6774691	*RBP2*	A	G	1.03(0.85, 1.25)	0.727	0.947
rs1902715	*RBP3*	A	G	1.02(0.85, 1.21)	0.856	0.984
rs10110749	*RDH10*	G	C	1.31(0.89, 1.94)	0.168	0.807
rs974456	*STRA6*	T	C	1.18(1.00, 1.39)	0.054	0.703
rs4393871	*RARB*	T	C	1.02(0.73, 1.43)	0.897	0.984
rs1123944	*RXRG*	T	C	0.82(0.63, 1.07)	0.146	0.784
rs7182884	*ALDH1A3*	C	A	1.15(0.85, 1.56)	0.374	0.904
rs17326524	*STRA6*	C	T	0.98(0.78, 1.24)	0.879	0.984
rs8031689	*CRABP1*	T	C	1.16(0.91, 1.48)	0.222	0.854
rs11204208	*RBP3*	T	G	1.12(0.89, 1.40)	0.336	0.891
rs10203870	*CYP26B1*	A	C	1.00(0.86, 1.18)	0.965	0.984
rs11185662	*RXRA*	C	T	1.10(0.92, 1.30)	0.300	0.876
rs11707637	*RARB*	G	A	1.05(0.76, 1.45)	0.781	0.973
rs295492	*RBP1*	T	C	1.16(0.98, 1.37)	0.088	0.778
rs7428398	*RBP1*	A	G	0.85(0.71, 1.00)	0.053	0.703
rs41356949	*RBP2*	T	C	0.92(0.65, 1.30)	0.638	0.935

RR: Risk ratio; **CI**: Confidence interval

SNP	Gene	Minor Allele	Major Allele	RR (95% CI)	P-value	Q-value
rs12929595	*BCMO1*	A	G	0.99(0.77, 1.27)	0.927	0.984
rs13325144	*RBP2*	A	G	0.99(0.84, 1.17)	0.884	0.984
rs1946518	*BCO2*	T	G	1.09(0.93, 1.29)	0.286	0.876
rs157865	*RXRG*	A	C	1.20(0.98, 1.48)	0.083	0.778
rs8187889	*ALDH1A1*	C	T	0.87(0.71, 1.06)	0.166	0.807
rs360722	*BCO2*	T	C	0.94(0.79, 1.11)	0.461	0.904
rs922939	*RARB*	G	T	0.77(0.65, 0.91)	0.003	0.274
rs3852534	*RDH5*	A	G	1.23(0.85, 1.77)	0.277	0.876
rs1968481	*RARB*	G	A	0.94(0.69, 1.27)	0.674	0.947
rs1286773	*RARB*	G	C	1.09(0.92, 1.29)	0.312	0.876
rs913422	*CYP26A1*	C	T	1.00(0.70, 1.42)	0.982	0.989
rs7289450	*ISX*	C	G	0.99(0.83, 1.16)	0.859	0.984
rs5744222	*BCO2*	A	C	1.09(0.83, 1.42)	0.549	0.917
rs1286738	*RARB*	T	C	0.92(0.74, 1.13)	0.414	0.904
rs875444	*RXRA*	G	A	0.93(0.79, 1.10)	0.384	0.904
rs17016584	*RARB*	G	C	1.05(0.87, 1.27)	0.607	0.927
rs7905501	*CYP26A1*	T	C	1.04(0.88, 1.23)	0.613	0.927
rs455696	*RXRG*	C	T	0.94(0.77, 1.13)	0.494	0.904
rs6738598	*CYP26B1*	G	A	0.88(0.68, 1.14)	0.325	0.882
rs6989495	*RDH10*	T	G	1.10(0.93, 1.30)	0.278	0.876
rs3821629	*RARB*	G	A	1.21(0.98, 1.50)	0.082	0.778
rs351219	*STRA6*	C	T	0.72(0.56, 0.93)	0.012	0.441
rs2072827	*ALDH8A1*	A	G	0.88(0.66, 1.19)	0.415	0.904
rs6537944	*RXRA*	C	T	1.24(0.93, 1.65)	0.139	0.784
rs517456	*RXRG*	C	G	0.99(0.83, 1.19)	0.932	0.984
rs755661	*RARB*	T	C	1.03(0.87, 1.21)	0.750	0.960
rs1154454	*ADH7*	C	T	1.05(0.82, 1.35)	0.701	0.947
rs7624894	*RARB*	C	T	0.98(0.73, 1.31)	0.883	0.984
rs11187545	*RBP4*	G	A	1.01(0.82, 1.23)	0.951	0.984
rs1547387	*RXRB*	C	G	1.14(0.94, 1.40)	0.192	0.820
rs4147531	*ADH1A*	T	C	1.27(1.01, 1.60)	0.041	0.696
rs156500	*LRAT*	C	A	1.01(0.85, 1.20)	0.880	0.984
rs11103603	*RXRA*	C	T	1.07(0.90, 1.27)	0.453	0.904
rs12635733	*RARB*	C	T	1.04(0.82, 1.32)	0.728	0.947
rs1128977	*RXRG*	T	C	1.08(0.91, 1.28)	0.375	0.904
rs3819197	*ADH1A*	T	C	1.01(0.85, 1.21)	0.885	0.984
rs7959622	*RDH5*	C	T	0.94(0.80, 1.12)	0.496	0.904
rs1506951	*RXRG*	T	C	0.97(0.79, 1.19)	0.742	0.952
rs17587689	*ADH7*	A	G	1.06(0.89, 1.27)	0.510	0.904
rs190910	*RBP1*	A	T	0.87(0.65, 1.16)	0.343	0.891
rs4889291	*BCMO1*	G	A	0.98(0.74, 1.31)	0.900	0.984
rs10776909	*RXRA*	T	C	0.98(0.78, 1.24)	0.891	0.984
rs9494108	*ALDH8A1*	T	C	1.07(0.90, 1.28)	0.442	0.904

RR: Risk ratio; **CI**: Confidence interval

SNP	Gene	Minor Allele	Major Allele	RR (95% CI)	P-value	Q-value
rs955243	*LRAT*	A	G	0.96(0.79, 1.17)	0.700	0.947
rs3010496	*PNLIP*	A	G	0.93(0.74, 1.18)	0.565	0.920
rs11187531	*RBP4*	C	T	0.99(0.85, 1.16)	0.942	0.984
rs10736370	*RBP3*	C	T	0.99(0.85, 1.16)	0.886	0.984
rs729147	*ADH7*	G	A	0.89(0.62, 1.28)	0.531	0.911
rs17525900	*RARB*	C	T	0.99(0.84, 1.18)	0.943	0.984
rs9886504	*RDH10*	A	G	0.95(0.71, 1.27)	0.739	0.951
rs925987	*CRABP1*	C	T	0.86(0.69, 1.06)	0.151	0.784
rs2413292	*ISX*	T	C	1.06(0.86, 1.29)	0.603	0.927
rs1154473	*ADH7*	T	C	0.89(0.75, 1.06)	0.204	0.854
rs7606254	*CYP26B1*	T	C	1.18(0.91, 1.53)	0.208	0.854
rs3138140	*RDH5*	A	G	0.83(0.66, 1.03)	0.097	0.778
rs11630924	*STRA6*	C	G	1.04(0.79, 1.37)	0.762	0.962
rs4681028	*RARB*	T	G	0.96(0.74, 1.25)	0.758	0.962
rs1154470	*ADH7*	A	G	0.96(0.79, 1.18)	0.709	0.947
rs17117895	*RDH5*	T	C	0.87(0.75, 1.02)	0.087	0.778
rs34571439	*RBP4*	C	A	0.97(0.79, 1.20)	0.786	0.977
rs10212330	*RARB*	A	T	1.02(0.86, 1.20)	0.854	0.984
rs12932003	*BCMO1*	G	A	0.95(0.81, 1.11)	0.522	0.911
rs7094671	*RBP4*	A	G	1.03(0.86, 1.23)	0.734	0.950
rs1800458	*TTR*	A	G	0.98(0.80, 1.19)	0.834	0.984
rs11187519	*RBP4*	A	C	1.08(0.86, 1.37)	0.496	0.904
rs9937350	*BCMO1*	C	T	1.01(0.85, 1.19)	0.928	0.984
rs7235277	*TTR*	C	G	1.06(0.90, 1.25)	0.508	0.904
rs12512714	*LRAT*	G	C	0.81(0.64, 1.04)	0.107	0.778
rs4887066	*STRA6*	T	C	0.78(0.60, 1.01)	0.058	0.703
rs3758538	*RBP4*	C	A	0.96(0.81, 1.14)	0.631	0.930
rs2041666	*CYP26B1*	A	C	1.04(0.88, 1.22)	0.667	0.947
rs1286764	*RARB*	A	T	0.98(0.72, 1.34)	0.895	0.984
rs2071025	*RXRB*	C	T	0.96(0.75, 1.21)	0.711	0.947
rs348464	*ALDH1A1*	T	A	0.93(0.79, 1.10)	0.407	0.904
rs12442054	*STRA6*	A	G	0.98(0.80, 1.20)	0.859	0.984
rs1286657	*RARB*	G	C	0.92(0.72, 1.18)	0.507	0.904
rs7291929	*ISX*	A	G	0.99(0.77, 1.26)	0.910	0.984
rs11214127	*BCO2*	A	G	0.95(0.77, 1.17)	0.630	0.930
rs6564863	*BCMO1*	T	C	0.91(0.70, 1.19)	0.500	0.904
rs6564864	*BCMO1*	T	G	0.94(0.79, 1.12)	0.466	0.904
rs7613553	*RARB*	A	C	1.18(0.93, 1.49)	0.176	0.807
rs6721368	*CYP26B1*	G	T	1.09(0.92, 1.29)	0.308	0.876
rs10518951	*ALDH1A2*	A	C	0.89(0.71, 1.11)	0.302	0.876
rs7637031	*RARB*	T	G	0.99(0.76, 1.29)	0.960	0.984
rs11214106	*BCO2*	C	T	0.81(0.62, 1.06)	0.129	0.784
rs3767342	*RXRG*	C	T	1.22(0.96, 1.56)	0.109	0.778

RR: Risk ratio; **CI**: Confidence interval

SNP	Gene	Minor Allele	Major Allele	RR (95% CI)	P-value	Q-value
rs3767343	*RXRG*	A	G	1.07(0.82, 1.40)	0.610	0.927
rs2012147	*ALDH1A2*	T	C	1.04(0.85, 1.27)	0.680	0.947
rs6835524	*ADH7*	T	C	0.98(0.78, 1.24)	0.894	0.984
rs7629478	*RARB*	G	T	0.88(0.75, 1.03)	0.122	0.784
rs3129200	*RXRB*	C	T	0.95(0.79, 1.14)	0.549	0.917
rs4349972	*RDH10*	T	C	1.12(0.90, 1.39)	0.319	0.876
rs4646870	*ALDH8A1*	T	G	1.08(0.84, 1.38)	0.539	0.911
rs6587052	*RBP3*	C	T	0.93(0.79, 1.09)	0.383	0.904
rs4657438	*RXRG*	C	A	0.83(0.69, 1.00)	0.044	0.696
rs707718	*CYP26B1*	A	C	0.85(0.70, 1.02)	0.085	0.778
rs3118529	*RXRA*	C	T	1.24(1.02, 1.52)	0.033	0.696
rs211585	*RBP1*	C	T	1.17(1.00, 1.38)	0.057	0.703
rs6580936	*RARG*	G	A	1.02(0.75, 1.37)	0.912	0.984
rs595958	*ALDH1A1*	A	G	0.93(0.77, 1.11)	0.417	0.904
rs4935984	*BCO2*	A	G	0.94(0.71, 1.25)	0.659	0.947
rs157862	*RXRG*	T	A	1.10(0.79, 1.53)	0.581	0.927
rs913423	*CYP26A1*	C	T	0.98(0.84, 1.15)	0.791	0.979
rs918776	*BCMO1*	T	C	1.04(0.88, 1.23)	0.652	0.947
rs41419946	*RXRG*	T	A	0.96(0.77, 1.20)	0.726	0.947
rs7768278	*ALDH8A1*	C	T	1.05(0.86, 1.29)	0.631	0.930
rs11776584	*RDH10*	A	G	0.85(0.72, 1.01)	0.066	0.754
rs284794	*ADH7*	T	A	1.12(0.86, 1.46)	0.394	0.904
rs4148887	*ADH4*	C	T	0.98(0.83, 1.16)	0.832	0.984
rs3772868	*RBP1*	T	C	1.02(0.85, 1.23)	0.811	0.984
rs12502290	*ADH7*	A	G	0.86(0.73, 1.02)	0.083	0.778
rs13085878	*RARB*	T	C	1.10(0.94, 1.30)	0.235	0.864
rs361741	*ISX*	T	C	1.01(0.86, 1.19)	0.910	0.984
rs3741434	*RARG*	G	A	1.16(0.95, 1.42)	0.150	0.784
rs12739596	*RXRG*	C	A	0.77(0.65, 0.91)	0.003	0.274
rs11103473	*RXRA*	T	A	1.07(0.79, 1.45)	0.664	0.947
rs11645428	*BCMO1*	A	G	1.00(0.85, 1.18)	0.968	0.984
rs11187529	*RBP4*	T	C	1.05(0.88, 1.24)	0.601	0.927
rs4922517	*RBP3*	T	G	0.89(0.72, 1.10)	0.276	0.876
rs1153603	*RARB*	A	G	0.93(0.76, 1.14)	0.484	0.904
rs7071684	*RBP3*	T	C	1.11(0.94, 1.31)	0.232	0.864
rs1367038	*BCO2*	C	A	0.96(0.81, 1.15)	0.678	0.947
rs1371338	*RBP2*	C	T	1.11(0.79, 1.56)	0.554	0.918
rs17529377	*ADH7*	C	T	1.24(0.87, 1.75)	0.228	0.864
rs8187876	*ALDH1A1*	A	G	1.08(0.88, 1.32)	0.453	0.904
rs7620852	*RARB*	C	T	0.91(0.76, 1.08)	0.285	0.876
rs16938613	*RDH10*	C	A	1.01(0.84, 1.23)	0.887	0.984
rs149225	*LRAT*	C	A	1.08(0.90, 1.29)	0.398	0.904
rs994772	*ADH7*	A	G	1.22(1.00, 1.49)	0.047	0.703

RR: Risk ratio; **CI**: Confidence interval

SNP	Gene	Minor Allele	Major Allele	RR (95% CI)	P-value	Q-value
rs4646607	*ALDH1A2*	T	G	0.78(0.64, 0.95)	0.012	0.441
rs11143419	*ALDH1A1*	C	G	0.87(0.73, 1.03)	0.104	0.778
rs2017362	*ALDH1A1*	T	C	0.86(0.72, 1.04)	0.114	0.784
rs2715554	*RARA*	C	T	0.83(0.64, 1.09)	0.176	0.807
rs2855425	*RXRB*	C	T	0.98(0.83, 1.16)	0.857	0.984
rs6426914	*RXRG*	G	A	1.15(0.97, 1.37)	0.106	0.778
rs1286769	*RARB*	T	C	1.10(0.71, 1.70)	0.683	0.947
rs1881705	*RARB*	G	A	1.05(0.89, 1.25)	0.560	0.919
rs10427677	*ISX*	C	A	1.29(1.09, 1.54)	0.004	0.274
rs6775425	*RARB*	C	T	0.88(0.71, 1.09)	0.245	0.876
rs3758494	*RBP3*	G	C	1.02(0.84, 1.24)	0.825	0.984
rs12903202	*ALDH1A2*	G	A	1.00(0.79, 1.26)	0.971	0.984
rs1626875	*RARB*	T	C	1.02(0.74, 1.39)	0.907	0.984
rs1286772	*RARB*	C	G	0.99(0.74, 1.34)	0.968	0.984
rs10048138	*BCMO1*	A	G	0.99(0.85, 1.17)	0.945	0.984
rs991316	*ADH7*	A	G	1.09(0.92, 1.29)	0.339	0.891
rs2925455	*RDH10*	C	A	0.97(0.82, 1.14)	0.713	0.947
rs7080494	*CYP26A1*	G	A	1.08(0.88, 1.33)	0.456	0.904
rs1583977	*ADH7*	T	A	0.98(0.71, 1.35)	0.900	0.984
rs11818333	*RBP3*	A	T	0.92(0.77, 1.09)	0.315	0.876
rs348463	*ALDH1A1*	C	T	1.04(0.84, 1.29)	0.701	0.947
rs283690	*RXRG*	G	A	0.89(0.67, 1.17)	0.393	0.904
rs17016773	*RARB*	T	C	1.07(0.90, 1.27)	0.443	0.904
rs4681027	*RARB*	G	T	1.01(0.86, 1.19)	0.889	0.984
rs6774124	*RARB*	G	C	0.82(0.69, 0.98)	0.026	0.609
rs3935542	*CRABP2*	G	C	0.83(0.69, 0.99)	0.036	0.696
rs1992005	*RARB*	T	C	0.79(0.67, 0.93)	0.006	0.274
rs2017543	*ISX*	C	T	1.15(0.98, 1.35)	0.094	0.778
rs4681063	*RARB*	C	T	0.94(0.79, 1.12)	0.488	0.904
rs2072915	*RXRB*	T	A	0.91(0.73, 1.13)	0.377	0.904
rs3138142	*RDH5*	A	G	1.02(0.85, 1.22)	0.854	0.984
rs3768647	*CYP26B1*	C	G	0.97(0.79, 1.19)	0.765	0.962
rs1154477	*ADH7*	T	C	1.24(0.88, 1.74)	0.214	0.854
rs1432603	*RARB*	C	T	0.79(0.56, 1.10)	0.161	0.807
rs11715516	*RARB*	G	C	0.99(0.78, 1.26)	0.935	0.984
rs736118	*STRA6*	T	C	0.94(0.79, 1.12)	0.507	0.904
rs7629902	*RARB*	A	G	0.94(0.79, 1.12)	0.484	0.904
rs3138144	*RDH5*	G	C	0.97(0.82, 1.14)	0.689	0.947
rs1435705	*RARB*	A	G	0.82(0.62, 1.08)	0.156	0.801
rs1286654	*RARB*	T	G	0.80(0.67, 0.97)	0.024	0.609
rs10882273	*RBP4*	C	T	0.84(0.71, 1.01)	0.060	0.708
rs1372369	*ALDH1A2*	C	A	1.20(0.96, 1.49)	0.111	0.778
rs11856111	*CRABP1*	C	T	1.40(1.14, 1.72)	0.001	0.274

RR: Risk ratio; **CI**: Confidence interval

SNP	Gene	Minor Allele	Major Allele	RR (95% CI)	P-value	Q-value
rs284789	*ADH7*	C	T	1.01(0.85, 1.19)	0.950	0.984
rs4646684	*ALDH1A3*	A	G	1.18(0.95, 1.47)	0.139	0.784
rs1303629	*RARB*	G	T	1.09(0.79, 1.51)	0.606	0.927
rs13070407	*RARB*	C	T	0.93(0.78, 1.11)	0.412	0.904
rs7039190	*RXRA*	C	A	1.02(0.80, 1.29)	0.893	0.984
rs3132301	*RXRA*	T	C	1.19(0.87, 1.62)	0.277	0.876
rs2462936	*RDH5*	T	C	1.27(1.06, 1.51)	0.008	0.340
rs17016781	*RARB*	G	A	0.99(0.69, 1.43)	0.962	0.984
rs2899611	*ALDH1A2*	G	T	0.93(0.79, 1.09)	0.381	0.904
rs1286665	*RARB*	T	C	1.08(0.87, 1.33)	0.492	0.904
rs17016778	*RARB*	G	A	0.95(0.81, 1.11)	0.512	0.904
rs7845956	*RDH10*	A	G	1.01(0.84, 1.22)	0.920	0.984
rs4144005	*ALDH1A2*	T	C	0.85(0.65, 1.11)	0.220	0.854
rs3814160	*RBP3*	T	C	1.07(0.82, 1.40)	0.598	0.927
rs11999628	*ALDH1A1*	T	G	1.06(0.89, 1.26)	0.530	0.911
rs11898950	*CYP26B1*	G	A	0.93(0.78, 1.11)	0.432	0.904
rs11187536	*RBP4*	T	G	1.04(0.87, 1.24)	0.694	0.947
rs12759184	*CRABP2*	T	C	1.08(0.89, 1.32)	0.425	0.904
rs9835241	*RBP1*	G	A	0.96(0.79, 1.16)	0.654	0.947
rs100537	*RXRG*	A	G	1.02(0.74, 1.39)	0.917	0.984
rs12934922	*BCMO1*	T	A	1.12(0.94, 1.34)	0.220	0.854
rs4418728	*CYP26A1*	T	G	0.80(0.61, 1.05)	0.110	0.778
rs11214125	*BCO2*	T	C	0.95(0.72, 1.25)	0.702	0.947
rs351229	*STRA6*	C	A	0.88(0.70, 1.11)	0.266	0.876
rs6564854	*BCMO1*	G	A	1.02(0.81, 1.29)	0.869	0.984
rs12442110	*CRABP1*	C	G	0.87(0.72, 1.06)	0.160	0.807
rs3806412	*CRABP2*	G	T	1.01(0.83, 1.23)	0.944	0.984
rs6776706	*RARB*	A	T	1.05(0.90, 1.24)	0.529	0.911
rs12578814	*RDH5*	A	G	1.10(0.93, 1.29)	0.262	0.876
rs1799908	*RXRB*	T	A	0.91(0.78, 1.08)	0.283	0.876
rs8027180	*CRABP1*	A	G	1.04(0.84, 1.29)	0.729	0.947
rs746332	*RXRG*	A	C	1.06(0.90, 1.25)	0.500	0.904
rs284792	*ADH7*	A	G	1.07(0.90, 1.26)	0.461	0.904
rs7620529	*RARB*	A	C	0.95(0.81, 1.13)	0.588	0.927
rs1286646	*RARB*	G	A	1.07(0.86, 1.34)	0.536	0.911
rs1881704	*RARB*	G	C	1.08(0.88, 1.33)	0.457	0.904
rs17016718	*RARB*	C	T	0.93(0.74, 1.18)	0.571	0.921
rs6564859	*BCMO1*	G	A	0.88(0.69, 1.13)	0.322	0.879
rs285428	*RXRG*	C	T	0.88(0.73, 1.06)	0.182	0.820
rs12915846	*STRA6*	A	G	1.07(0.83, 1.38)	0.602	0.927
rs8187910	*ALDH1A1*	G	A	0.94(0.80, 1.11)	0.497	0.904
rs11635868	*STRA6*	T	C	1.08(0.86, 1.35)	0.518	0.911
rs12249434	*PNLIP*	T	C	1.06(0.88, 1.27)	0.549	0.917

RR: Risk ratio; **CI**: Confidence interval

SNP	Gene	Minor Allele	Major Allele	RR (95% CI)	P-value	Q-value
rs1286730	*RARB*	G	C	0.95(0.80, 1.13)	0.581	0.927
rs4384231	*CRABP2*	T	C	1.00(0.68, 1.46)	0.990	0.994
rs213210	*RXRB*	C	T	0.85(0.69, 1.05)	0.132	0.784
rs2192332	*CYP26B1*	G	T	1.08(0.92, 1.28)	0.346	0.892
rs12256889	*CYP26C1*	A	C	0.97(0.66, 1.40)	0.853	0.984
rs4889293	*BCMO1*	G	C	0.92(0.78, 1.08)	0.317	0.876
rs10786068	*CYP26A1*	C	G	0.95(0.81, 1.12)	0.555	0.918
rs17016408	*RARB*	C	G	1.04(0.84, 1.30)	0.701	0.947
rs5999690	*ISX*	C	T	0.77(0.57, 1.06)	0.110	0.778
rs17029657	*RARB*	G	T	0.92(0.67, 1.27)	0.616	0.927
rs7324	*CEL*	A	G	0.90(0.62, 1.32)	0.602	0.927
rs4646615	*ALDH1A2*	T	G	1.03(0.78, 1.37)	0.812	0.984
rs3757971	*DGAT1*	G	A	0.94(0.64, 1.40)	0.768	0.963
rs7621140	*RARB*	C	T	0.84(0.53, 1.33)	0.457	0.904
rs4607073	*RARB*	G	T	0.78(0.66, 0.93)	0.005	0.274
rs1286754	*RARB*	T	C	0.95(0.80, 1.13)	0.567	0.920
rs9821204	*RBP1*	A	C	0.93(0.75, 1.14)	0.476	0.904
rs9871002	*RARB*	T	A	0.96(0.81, 1.13)	0.608	0.927
rs2272301	*RARG*	G	C	0.92(0.78, 1.08)	0.313	0.876
rs2654848	*ADH7*	A	T	1.11(0.94, 1.31)	0.234	0.864
rs12169293	*ISX*	A	G	1.03(0.87, 1.21)	0.738	0.951
rs8187950	*ALDH1A1*	C	T	0.92(0.77, 1.09)	0.332	0.889
rs10489745	*RXRG*	C	T	0.98(0.84, 1.16)	0.853	0.984
rs1286641	*RARB*	T	A	0.83(0.70, 0.98)	0.024	0.609
rs3138136	*RDH5*	A	G	0.87(0.65, 1.17)	0.362	0.904
rs11642457	*BCMO1*	G	A	1.01(0.74, 1.37)	0.952	0.984
rs9934274	*BCMO1*	G	C	1.07(0.91, 1.26)	0.421	0.904
rs13099641	*RARB*	A	T	0.97(0.82, 1.14)	0.711	0.947
rs7187507	*BCMO1*	T	A	1.05(0.88, 1.26)	0.556	0.918
rs2602884	*ADH4*	C	T	1.03(0.86, 1.24)	0.721	0.947
rs1888202	*ALDH1A1*	G	C	1.06(0.83, 1.34)	0.639	0.935
rs7620632	*RARB*	C	T	1.11(0.91, 1.36)	0.289	0.876
rs6518932	*ISX*	T	C	1.00(0.82, 1.21)	0.969	0.984
rs3764478	*TTR*	A	C	1.15(0.92, 1.45)	0.223	0.854
rs10800091	*RXRG*	G	A	0.86(0.69, 1.09)	0.210	0.854
rs1483856	*RARB*	C	A	0.93(0.76, 1.14)	0.496	0.904
rs34745537	*RARG*	A	G	0.97(0.83, 1.14)	0.755	0.962
rs1286766	*RARB*	T	A	0.94(0.80, 1.11)	0.464	0.904
rs1997353	*RARB*	G	A	0.82(0.68, 0.98)	0.033	0.696
rs7616467	*RARB*	T	C	0.81(0.57, 1.16)	0.260	0.876
rs887844	*CYP26B1*	C	T	1.05(0.81, 1.36)	0.724	0.947

RR: Risk ratio; **CI**: Confidence interval

APPENDIX 3. RESULTS FROM OFFSPRING FOLATE AND CHOLINE-RELATED SNPS IN NENA AND CHOP REPLICATION STUDY

		NENA					CHOP				
SNP	Gene	Minor Allele	Major Allele	RR 95%(CI)	P-value	FDR Q-value	Minor Allele	Major Allele	OR 95%(CI)	P-value	FDR Q-value
rs3123634	*SLC22A3*	T	C	1.34(1.14, 1.58)	0.001	0.459	T	C	1.00(0.93, 1.09)	0.941	0.986
rs2302327	*PLD2*	A	G	1.70(1.23, 2.34)	0.001	0.502	T	C	0.90(0.77, 1.04)	0.158	0.854
rs316174	*SLC22A3*	T	C	1.30(1.10, 1.54)	0.002	0.502	G	A	1.02(0.94, 1.10)	0.621	0.969
rs803456	*MTHFD1L*	C	T	0.78(0.66, 0.92)	0.003	0.621	G	A	0.99(0.92, 1.08)	0.888	0.979
rs663649	*CTH*	T	G	1.30(1.08, 1.57)	0.006	0.785	T	G	1.06(0.97, 1.15)	0.173	0.866
rs4869087	*MAT2B*	C	A	1.29(1.07, 1.55)	0.007	0.785	A	C	0.95(0.87, 1.04)	0.285	0.909
rs17421462	*MTHFR*	A	G	0.65(0.48, 0.89)	0.007	0.785	A	G	1.01(0.88, 1.17)	0.865	0.979
rs604745	*SLC44A5*	G	T	0.76(0.62, 0.94)	0.010	0.785	A	C	0.93(0.85, 1.02)	0.146	0.839
rs3797546	*BHMT*	C	T	1.65(1.12, 2.44)	0.012	0.785	C	T	1.03(0.84, 1.26)	0.799	0.979
rs2221750	*SLC22A3*	A	G	1.29(1.05, 1.58)	0.014	0.785	T	C	1.00(0.90, 1.10)	0.936	0.986
rs2424922	*DNMT3B*	C	T	1.23(1.04, 1.46)	0.016	0.785	C	T	1.03(0.95, 1.11)	0.511	0.965
rs17806489	*SHMT1*	A	G	0.73(0.56, 0.94)	0.017	0.785	A	G	1.09(0.96, 1.24)	0.174	0.866
rs11202403	*MAT1A*	T	C	1.29(1.05, 1.59)	0.017	0.785	T	C	1.08(0.98, 1.19)	0.136	0.839
rs2083868	*SLC44A5*	G	A	0.79(0.65, 0.96)	0.018	0.785	C	T	0.98(0.90, 1.07)	0.689	0.972
rs4819208	*FTCD*	G	A	1.28(1.04, 1.57)	0.018	0.785	A	G	1.01(0.93, 1.11)	0.773	0.979
rs7642538	*ALDH1L1*	A	G	0.79(0.65, 0.96)	0.018	0.785	--	--	--	--	--
rs712208	*MTHFD1L*	T	C	0.78(0.63, 0.96)	0.019	0.785	A	G	0.96(0.87, 1.06)	0.394	0.948
rs7733775	*MAT2B*	A	G	1.22(1.03, 1.45)	0.019	0.785	G	A	1.00(0.92, 1.08)	0.996	0.998
rs17080476	*MTHFD1L*	G	A	0.77(0.62, 0.96)	0.019	0.785	G	A	0.99(0.90, 1.10)	0.890	0.979
rs4708867	*SLC22A3*	G	A	1.38(1.05, 1.80)	0.021	0.785	G	A	1.00(0.88, 1.14)	0.976	0.996
rs1979277	*SHMT1*	A	G	1.23(1.03, 1.47)	0.022	0.785	A	G	0.97(0.89, 1.05)	0.442	0.962
rs2504937	*SLC22A3*	G	C	0.81(0.68, 0.97)	0.023	0.785	G	C	0.99(0.91, 1.08)	0.785	0.979
rs2504956	*SLC22A3*	A	G	0.78(0.63, 0.97)	0.023	0.785	T	C	0.98(0.89, 1.09)	0.755	0.979
rs13373826	*SLC44A5*	G	A	0.76(0.60, 0.97)	0.024	0.785	G	A	0.97(0.87, 1.08)	0.600	0.969
rs1650697	*DHFR*	T	C	0.80(0.65, 0.97)	0.027	0.785	G	A	0.97(0.88, 1.06)	0.476	0.963
rs1967613	*ATIC*	A	T	1.22(1.02, 1.46)	0.029	0.785	T	A	1.00(0.92, 1.09)	0.965	0.993
rs7604984	*ATIC*	G	A	1.20(1.02, 1.42)	0.029	0.785	A	G	0.98(0.91, 1.06)	0.668	0.971
rs17375901	*MTHFR*	T	C	1.51(1.03, 2.20)	0.033	0.785	T	C	0.88(0.74, 1.05)	0.151	0.839
rs4646703	*ALDH1L1*	A	G	0.77(0.61, 0.98)	0.033	0.785	--	--	--	--	--
rs512077	*SLC22A3*	A	G	1.27(1.02, 1.59)	0.034	0.785	G	A	1.09(0.97, 1.22)	0.141	0.839
rs3798156	*SLC22A2*	A	G	1.32(1.02, 1.70)	0.034	0.785	T	C	0.99(0.88, 1.12)	0.901	0.979

RR: Risk Ratio; **CI**: Confidence Interval; **OR**: Odds Ratio; --: Unavailable in replication study

		NENA					CHOP				
SNP	Gene	Minor Allele	Major Allele	RR 95%(CI)	P-value	FDR Q-value	Minor Allele	Major Allele	OR 95%(CI)	P-value	FDR Q-value
rs519861	*MTHFD1L*	C	T	1.26(1.02, 1.56)	0.035	0.785	A	G	0.99(0.90, 1.09)	0.839	0.979
rs3120137	*SLC22A3*	T	C	1.31(1.02, 1.68)	0.036	0.785	A	G	0.95(0.85, 1.06)	0.347	0.943
rs1004053	*SLC44A5*	G	A	0.83(0.70, 0.99)	0.036	0.785	T	C	0.99(0.92, 1.07)	0.804	0.979
rs7722729	*MAT2B*	C	T	1.27(1.01, 1.58)	0.038	0.785	C	T	0.97(0.87, 1.08)	0.614	0.969
rs627494	*SLC44A5*	G	T	0.84(0.71, 0.99)	0.039	0.785	G	T	1.01(0.94, 1.09)	0.779	0.979
rs661620	*DMGDH*	C	T	0.84(0.71, 0.99)	0.041	0.785	C	T	0.98(0.91, 1.06)	0.654	0.971
rs2283124	*SARDH*	T	C	1.31(1.01, 1.71)	0.042	0.785	--	--	--	--	--
rs11663153	*TYMS*	A	C	1.22(1.01, 1.48)	0.043	0.785	A	C	1.11(1.00, 1.24)	0.051	0.823
rs17591295	*SLC22A3*	A	G	1.47(1.01, 2.14)	0.045	0.785	A	G	0.99(0.82, 1.19)	0.929	0.983
rs2048327	*SLC22A3*	G	A	1.20(1.00, 1.42)	0.046	0.785	C	T	0.94(0.87, 1.02)	0.150	0.839
rs28365862	*SHMT2*	G	A	1.48(1.01, 2.18)	0.046	0.785	--	--	--	--	--
rs1771845	*MTHFD1L*	T	C	0.84(0.71, 1.00)	0.046	0.785	A	G	0.94(0.87, 1.02)	0.142	0.839
rs11040265	*FOLH1*	T	C	1.34(1.00, 1.79)	0.047	0.785	--	--	--	--	--
rs3127575	*SLC22A2*	T	C	1.30(1.00, 1.70)	0.048	0.785	T	C	0.93(0.82, 1.05)	0.241	0.901
rs12995526	*ATIC*	T	C	0.85(0.72, 1.00)	0.048	0.785	C	T	1.06(0.98, 1.15)	0.135	0.839
rs3918227	*NOS3*	A	C	1.36(1.00, 1.86)	0.048	0.785	A	C	1.03(0.90, 1.18)	0.711	0.979
rs129886	*SARDH*	T	C	0.82(0.68, 1.00)	0.049	0.785	--	--	--	--	--
rs8016556	*MTHFD1*	C	T	0.84(0.71, 1.00)	0.049	0.785	C	T	0.97(0.89, 1.05)	0.467	0.963
rs8127036	*CBS*	T	C	0.79(0.63, 1.00)	0.050	0.785	T	C	0.94(0.85, 1.04)	0.261	0.905
rs11755049	*MTHFD1L*	T	A	0.76(0.58, 1.00)	0.052	0.785	T	A	0.94(0.82, 1.07)	0.332	0.943
rs4709432	*SLC22A3*	G	A	1.24(1.00, 1.55)	0.053	0.785	G	A	1.10(0.99, 1.23)	0.082	0.831
rs891512	*NOS3*	A	G	0.82(0.66, 1.00)	0.054	0.785	G	A	1.02(0.93, 1.13)	0.635	0.969
rs7081756	*MAT1A*	G	T	1.18(1.00, 1.40)	0.055	0.785	T	G	1.00(0.92, 1.08)	0.960	0.993
rs2273027	*SHMT1*	A	G	0.85(0.71, 1.00)	0.055	0.785	T	C	1.03(0.95, 1.12)	0.483	0.963
rs1205349	*AHCY*	C	G	1.27(0.99, 1.63)	0.056	0.785	--	--	--	--	--
rs316169	*SLC22A3*	A	C	1.19(1.00, 1.42)	0.056	0.785	G	T	1.02(0.93, 1.11)	0.702	0.977
rs11908812	*FTCD*	A	G	1.33(0.99, 1.78)	0.056	0.785	A	G	1.02(0.88, 1.18)	0.798	0.979
rs10821578	*SARDH*	T	C	1.17(1.00, 1.37)	0.056	0.785	--	--	--	--	--
rs140514	*CHKB*	C	T	1.17(1.00, 1.38)	0.057	0.785	G	A	0.94(0.86, 1.01)	0.096	0.831
rs11080058	*SLC46A1*	A	G	0.84(0.69, 1.01)	0.057	0.785	A	G	0.94(0.86, 1.03)	0.177	0.871
rs13063848	*PLD1*	A	G	1.31(0.99, 1.73)	0.057	0.785	A	G	1.10(0.98, 1.24)	0.120	0.837
rs7556057	*SLC44A5*	T	C	0.83(0.69, 1.01)	0.057	0.785	T	C	1.09(1.00, 1.19)	0.051	0.823
rs1544920	*CHPT1*	T	C	0.79(0.61, 1.01)	0.058	0.785	--	--	--	--	--
rs3755817	*CHDH*	C	T	1.19(0.99, 1.43)	0.059	0.785	C	T	0.98(0.90, 1.07)	0.636	0.969
rs2457552	*SLC22A3*	T	G	0.82(0.67, 1.01)	0.060	0.785	C	A	0.99(0.91, 1.09)	0.909	0.979

RR: Risk Ratio; **CI**: Confidence Interval; **OR**: Odds Ratio; --: Unavailable in replication study

		NENA					CHOP				
SNP	Gene	Minor Allele	Major Allele	RR 95%(CI)	P-value	FDR Q-value	Minor Allele	Major Allele	OR 95%(CI)	P-value	FDR Q-value
rs13317328	*CHDH*	C	A	0.77(0.58, 1.01)	0.061	0.785	C	A	1.05(0.90, 1.23)	0.500	0.963
rs612893	*DMGDH*	A	G	0.85(0.72, 1.01)	0.061	0.785	G	A	1.05(0.97, 1.14)	0.240	0.901
rs2303080	*MTRR*	A	T	1.55(0.98, 2.47)	0.062	0.785	A	T	0.82(0.65, 1.02)	0.080	0.831
rs3733890	*BHMT*	A	G	0.84(0.70, 1.01)	0.065	0.812	A	G	1.00(0.92, 1.09)	0.994	0.998
rs2909854	*BHMT*	C	G	0.85(0.71, 1.01)	0.067	0.829	--	--	--	--	--
rs1567441	*SLC22A3*	G	A	0.83(0.68, 1.01)	0.069	0.833	C	T	0.98(0.89, 1.07)	0.639	0.969
rs7533315	*MTHFR*	T	C	0.84(0.69, 1.02)	0.071	0.833	C	T	0.96(0.88, 1.06)	0.440	0.962
rs1891902	*SLC44A5*	T	C	0.85(0.71, 1.01)	0.072	0.833	A	G	1.00(0.92, 1.09)	0.975	0.996
rs2295638	*MTHFD1*	T	C	0.66(0.42, 1.04)	0.072	0.833	A	G	1.20(0.94, 1.53)	0.152	0.839
rs569919	*SLC22A3*	T	C	0.84(0.70, 1.02)	0.076	0.833	T	C	1.00(0.92, 1.09)	0.958	0.993
rs1950902	*MTHFD1*	T	C	0.82(0.66, 1.02)	0.078	0.833	G	A	1.05(0.94, 1.16)	0.391	0.948
rs3788190	*SLC19A1*	A	G	0.86(0.73, 1.02)	0.079	0.833	A	G	1.00(0.92, 1.08)	0.941	0.986
rs6753886	*SLC5A7*	A	G	0.86(0.72, 1.02)	0.081	0.833	A	G	0.97(0.90, 1.06)	0.537	0.969
rs10515861	*MAT2B*	C	T	0.85(0.71, 1.02)	0.083	0.833	C	T	1.02(0.94, 1.11)	0.622	0.969
rs1112444	*SLC22A3*	A	C	1.18(0.98, 1.42)	0.083	0.833	A	C	1.02(0.93, 1.11)	0.723	0.979
rs17588242	*SLC22A2*	C	T	0.84(0.69, 1.02)	0.083	0.833	C	T	1.06(0.96, 1.18)	0.243	0.901
rs803455	*MTHFD1L*	T	C	0.73(0.51, 1.04)	0.083	0.833	G	A	0.92(0.78, 1.07)	0.282	0.909
rs11595587	*MAT1A*	A	G	0.63(0.37, 1.06)	0.084	0.833	A	G	0.90(0.71, 1.14)	0.380	0.948
rs11664283	*TYMS*	A	G	1.18(0.98, 1.43)	0.086	0.833	A	G	1.06(0.97, 1.15)	0.216	0.892
rs17080461	*MTHFD1L*	T	C	0.80(0.61, 1.03)	0.088	0.833	T	C	0.96(0.84, 1.09)	0.515	0.965
rs492842	*BHMT*	G	A	0.87(0.73, 1.02)	0.090	0.833	T	C	1.02(0.94, 1.11)	0.575	0.969
rs4847361	*SLC44A3*	C	T	0.81(0.63, 1.03)	0.091	0.833	T	C	0.89(0.78, 1.02)	0.092	0.831
rs2137407	*SLC44A5*	A	G	1.41(0.95, 2.11)	0.091	0.833	T	C	0.87(0.71, 1.06)	0.171	0.862
rs7289549	*TCN2*	C	G	1.23(0.97, 1.57)	0.092	0.833	C	G	1.10(0.97, 1.26)	0.142	0.839
rs3794186	*CHKA*	T	C	1.33(0.95, 1.86)	0.092	0.833	A	G	0.81(0.70, 0.95)	0.009	0.446
rs2304429	*DNMT3A*	G	A	0.86(0.73, 1.02)	0.093	0.833	T	C	0.97(0.90, 1.05)	0.506	0.965
rs316176	*SLC22A3*	G	A	0.86(0.72, 1.03)	0.094	0.833	C	T	1.04(0.95, 1.13)	0.421	0.959
rs6668699	*MTHFR*	C	T	0.86(0.73, 1.03)	0.095	0.833	T	C	0.98(0.90, 1.06)	0.582	0.969
rs4846048	*MTHFR*	G	A	0.86(0.72, 1.03)	0.095	0.833	A	G	0.99(0.91, 1.08)	0.800	0.979
rs8019804	*MTHFD1*	G	T	1.32(0.95, 1.84)	0.095	0.833	T	G	0.96(0.83, 1.12)	0.637	0.969
rs6814380	*MTHFD2L*	G	C	1.16(0.98, 1.37)	0.095	0.833	G	C	1.06(0.97, 1.15)	0.195	0.891
rs299299	*MAT2B*	G	T	1.20(0.97, 1.50)	0.095	0.833	G	T	1.05(0.95, 1.17)	0.339	0.943
rs1580820	*PCYT1A*	C	T	0.81(0.63, 1.04)	0.095	0.833	A	G	0.99(0.88, 1.11)	0.811	0.979
rs7730643	*MTRR*	G	A	1.21(0.97, 1.52)	0.096	0.833	G	A	1.06(0.96, 1.18)	0.250	0.902
rs2287779	*MTRR*	A	G	1.43(0.93, 2.18)	0.100	0.833	A	G	0.84(0.68, 1.05)	0.122	0.837

RR: Risk Ratio; **CI**: Confidence Interval; **OR**: Odds Ratio; --: Unavailable in replication study

		NENA					CHOP				
SNP	Gene	Minor Allele	Major Allele	RR 95%(CI)	P-value	FDR Q-value	Minor Allele	Major Allele	OR 95%(CI)	P-value	FDR Q-value
rs248381	*DMGDH*	A	G	1.15(0.97, 1.35)	0.100	0.833	A	G	1.06(0.98, 1.14)	0.164	0.854
rs1249655	*SLC44A5*	A	T	1.16(0.97, 1.39)	0.101	0.833	T	A	0.95(0.88, 1.03)	0.242	0.901
rs140516	*CHKB*	A	G	1.18(0.97, 1.45)	0.101	0.833	C	T	0.91(0.83, 0.99)	0.036	0.756
rs9687295	*DMGDH*	G	A	0.83(0.66, 1.04)	0.102	0.833	G	A	0.97(0.87, 1.08)	0.556	0.969
rs17689595	*SLC22A5*	A	G	0.83(0.67, 1.04)	0.102	0.833	A	G	1.02(0.91, 1.15)	0.695	0.973
rs819144	*AHCY*	T	G	1.24(0.96, 1.60)	0.102	0.833	G	T	0.98(0.86, 1.10)	0.695	0.973
rs2007053	*GART*	C	T	1.18(0.97, 1.44)	0.104	0.833	T	C	1.04(0.95, 1.14)	0.384	0.948
rs2424932	*DNMT3B*	A	G	0.87(0.73, 1.03)	0.105	0.833	G	A	1.04(0.96, 1.13)	0.352	0.943
rs9669539	*CHPT1*	C	T	1.17(0.97, 1.40)	0.105	0.833	--	--	--	--	--
rs505358	*MTHFD1L*	T	C	1.16(0.97, 1.38)	0.106	0.833	A	G	0.99(0.91, 1.08)	0.838	0.979
rs7545324	*SLC44A5*	G	A	1.18(0.96, 1.45)	0.107	0.835	G	A	1.02(0.93, 1.13)	0.638	0.969
rs17269293	*SLC5A7*	G	C	1.19(0.96, 1.48)	0.109	0.843	G	C	0.96(0.86, 1.06)	0.376	0.948
rs333241	*SLC5A7*	T	C	0.85(0.69, 1.04)	0.112	0.861	G	A	1.03(0.94, 1.14)	0.498	0.963
rs939885	*PCYT1A*	G	A	0.88(0.75, 1.03)	0.114	0.864	A	G	0.97(0.89, 1.05)	0.459	0.963
rs10791958	*CHKA*	T	A	1.24(0.95, 1.63)	0.114	0.864	A	T	1.05(0.92, 1.19)	0.457	0.963
rs9968875	*MTHFD1L*	G	A	0.81(0.63, 1.05)	0.117	0.876	G	A	0.96(0.85, 1.08)	0.522	0.967
rs2298582	*TYMS*	C	A	0.82(0.64, 1.05)	0.118	0.876	G	T	1.05(0.90, 1.23)	0.540	0.969
rs8130986	*CBS*	A	G	1.23(0.95, 1.58)	0.120	0.886	A	G	0.92(0.81, 1.04)	0.170	0.862
rs11163496	*SLC44A5*	T	C	0.85(0.68, 1.05)	0.126	0.920	T	C	0.98(0.89, 1.09)	0.712	0.979
rs10265237	*NOS3*	A	G	1.16(0.96, 1.39)	0.127	0.922	A	G	0.99(0.90, 1.09)	0.847	0.979
rs1363730	*MAT2B*	T	C	1.20(0.94, 1.54)	0.141	0.945	T	C	1.05(0.93, 1.18)	0.467	0.963
rs162889	*SLC22A4*	T	C	0.87(0.72, 1.05)	0.141	0.945	T	C	1.03(0.94, 1.13)	0.540	0.969
rs17354394	*MTHFD1L*	G	A	1.28(0.92, 1.78)	0.142	0.945	G	A	1.02(0.87, 1.20)	0.794	0.979
rs12217395	*MAT1A*	A	G	1.15(0.95, 1.38)	0.142	0.945	A	G	1.09(0.99, 1.19)	0.068	0.831
rs1537514	*MTHFR*	G	C	1.23(0.93, 1.62)	0.143	0.945	C	G	0.95(0.83, 1.08)	0.398	0.949
rs2236225	*MTHFD1*	T	C	1.13(0.96, 1.33)	0.143	0.945	A	G	1.02(0.94, 1.10)	0.623	0.969
rs17448447	*ATIC*	G	A	1.14(0.96, 1.35)	0.144	0.945	G	A	1.03(0.95, 1.12)	0.500	0.963
rs705415	*DMGDH*	A	G	1.21(0.94, 1.57)	0.144	0.945	T	C	1.05(0.91, 1.21)	0.499	0.963
rs16879334	*MTRR*	G	C	1.37(0.90, 2.11)	0.146	0.945	G	C	0.84(0.68, 1.05)	0.122	0.837
rs4869713	*MTHFD1L*	C	T	0.88(0.75, 1.04)	0.146	0.945	T	C	1.01(0.93, 1.09)	0.894	0.979
rs4934028	*MAT1A*	A	G	0.88(0.75, 1.04)	0.147	0.945	A	G	0.96(0.89, 1.04)	0.366	0.948
rs4659718	*MTR*	C	A	0.88(0.74, 1.05)	0.148	0.945	A	C	1.03(0.95, 1.12)	0.432	0.962
rs9397365	*MTHFD1L*	T	C	0.84(0.67, 1.06)	0.148	0.945	T	C	1.13(1.00, 1.28)	0.046	0.823
rs16876394	*DMGDH*	C	T	1.23(0.93, 1.63)	0.149	0.945	C	T	1.02(0.90, 1.16)	0.730	0.979
rs12626309	*GART*	T	A	0.86(0.70, 1.05)	0.149	0.945	T	A	0.95(0.87, 1.05)	0.308	0.927

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		NENA					CHOP				
SNP	Gene	Minor Allele	Major Allele	RR 95%(CI)	P-value	FDR Q-value	Minor Allele	Major Allele	OR 95%(CI)	P-value	FDR Q-value
rs1073083	*CHPT1*	T	A	0.87(0.71, 1.05)	0.149	0.945	--	--	--	--	--
rs9478918	*MTHFD1L*	T	C	0.83(0.65, 1.07)	0.150	0.945	C	T	0.98(0.88, 1.10)	0.778	0.979
rs472703	*MTHFD1L*	G	A	0.85(0.68, 1.06)	0.151	0.945	C	T	0.98(0.88, 1.10)	0.764	0.979
rs698966	*SLC44A3*	G	T	0.88(0.75, 1.05)	0.152	0.945	A	C	0.96(0.89, 1.04)	0.318	0.934
rs1232027	*DHFR*	A	G	1.14(0.95, 1.35)	0.153	0.945	A	G	0.98(0.91, 1.07)	0.699	0.977
rs12637288	*PCYT1A*	G	A	0.89(0.75, 1.05)	0.154	0.945	A	G	1.00(0.93, 1.08)	0.950	0.988
rs250513	*DMGDH*	T	C	0.87(0.72, 1.06)	0.156	0.945	T	C	1.03(0.94, 1.13)	0.564	0.969
rs12275064	*FOLH1*	T	G	1.19(0.94, 1.51)	0.158	0.945	--	--	--	--	--
rs884534	*PCYT1A*	T	C	0.87(0.71, 1.06)	0.159	0.945	G	A	0.98(0.89, 1.07)	0.619	0.969
rs2041149	*CHPT1*	G	A	1.13(0.95, 1.34)	0.160	0.945	G	A	1.00(0.92, 1.08)	0.997	0.998
rs2797836	*SARDH*	A	G	1.12(0.96, 1.32)	0.161	0.945	--	--	--	--	--
rs514933	*FOLR2*	G	A	1.13(0.95, 1.33)	0.163	0.945	C	T	1.01(0.93, 1.10)	0.748	0.979
rs735937	*SLC44A3*	G	A	1.13(0.95, 1.33)	0.163	0.945	C	T	1.01(0.93, 1.09)	0.885	0.979
rs476235	*SLC22A2*	T	C	0.88(0.74, 1.05)	0.164	0.945	A	G	0.95(0.88, 1.03)	0.257	0.905
rs42418	*DMGDH*	G	C	1.12(0.95, 1.32)	0.164	0.945	C	G	0.99(0.91, 1.07)	0.765	0.979
rs12037733	*SLC44A3*	A	G	0.87(0.71, 1.06)	0.164	0.945	A	G	1.13(1.03, 1.25)	0.012	0.502
rs576075	*SLC22A2*	T	C	0.88(0.73, 1.05)	0.165	0.945	T	C	1.03(0.95, 1.12)	0.488	0.963
rs175853	*MTHFD1L*	T	C	1.13(0.95, 1.35)	0.167	0.951	G	A	1.03(0.95, 1.12)	0.518	0.967
rs12733999	*CTH*	T	C	1.36(0.88, 2.10)	0.169	0.951	T	C	1.00(0.84, 1.20)	0.971	0.995
rs9306264	*TCN2*	T	C	1.23(0.91, 1.66)	0.169	0.951	T	C	0.97(0.82, 1.15)	0.730	0.979
rs742829	*MTHFD1L*	G	A	1.16(0.94, 1.44)	0.173	0.957	C	T	0.92(0.82, 1.03)	0.137	0.839
rs2295640	*MTHFD1*	G	C	0.82(0.62, 1.09)	0.173	0.957	G	C	1.07(0.93, 1.23)	0.351	0.943
rs17520351	*SLC44A3*	T	C	0.79(0.57, 1.11)	0.178	0.964	T	C	1.01(0.86, 1.17)	0.944	0.986
rs12469531	*SLC5A7*	C	T	0.80(0.57, 1.11)	0.178	0.964	C	T	0.88(0.72, 1.06)	0.175	0.866
rs4270463	*ALDH1L1*	T	C	1.31(0.88, 1.95)	0.179	0.964	--	--	--	--	--
rs1036145	*NOS3*	A	G	0.89(0.75, 1.06)	0.181	0.964	T	C	1.03(0.95, 1.11)	0.539	0.969
rs642013	*DMGDH*	T	C	0.89(0.74, 1.06)	0.185	0.964	G	A	1.05(0.97, 1.15)	0.244	0.902
rs1570191	*MTHFD1L*	C	T	1.22(0.91, 1.64)	0.186	0.964	G	A	0.97(0.85, 1.11)	0.652	0.971
rs2741186	*TYMS*	T	C	0.90(0.76, 1.06)	0.192	0.964	G	A	0.98(0.92, 1.05)	0.604	0.969
rs7770982	*MTHFD1L*	G	A	0.84(0.64, 1.09)	0.193	0.964	G	A	1.03(0.91, 1.17)	0.628	0.969
rs2695284	*CHPT1*	C	T	0.90(0.76, 1.06)	0.199	0.964	A	G	1.01(0.93, 1.09)	0.886	0.979
rs6893970	*BHMT*	A	G	1.20(0.91, 1.57)	0.200	0.964	A	G	1.04(0.92, 1.18)	0.558	0.969
rs4911263	*DNMT3B*	T	C	0.89(0.74, 1.06)	0.200	0.964	C	T	1.05(0.96, 1.14)	0.303	0.927
rs906713	*CHKA*	A	G	0.87(0.70, 1.08)	0.200	0.964	G	A	0.98(0.88, 1.09)	0.709	0.979
rs1915706	*BHMT*	T	C	1.12(0.94, 1.33)	0.201	0.964	T	C	1.00(0.92, 1.08)	0.944	0.986

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		NENA					CHOP				
SNP	Gene	Minor Allele	Major Allele	RR 95%(CI)	P-value	FDR Q-value	Minor Allele	Major Allele	OR 95%(CI)	P-value	FDR Q-value
rs11185518	*PCYT1A*	T	C	0.86(0.68, 1.08)	0.203	0.964	T	C	0.97(0.87, 1.08)	0.577	0.969
rs2853741	*TYMS*	T	C	1.12(0.94, 1.33)	0.204	0.964	C	T	1.08(0.99, 1.19)	0.078	0.831
rs698964	*SLC44A3*	A	G	1.12(0.94, 1.33)	0.207	0.964	C	T	0.98(0.90, 1.06)	0.584	0.969
rs129902	*SARDH*	C	G	1.16(0.92, 1.45)	0.211	0.964	--	--	--	--	--
rs6058897	*DNMT3B*	A	C	0.90(0.76, 1.06)	0.213	0.964	C	A	1.06(0.98, 1.15)	0.119	0.837
rs175860	*MTHFD1L*	A	C	0.90(0.76, 1.06)	0.214	0.964	G	T	1.07(0.99, 1.16)	0.107	0.837
rs4911107	*DNMT3B*	A	G	1.11(0.94, 1.31)	0.214	0.964	A	G	1.03(0.95, 1.11)	0.496	0.963
rs12745827	*CEPT1*	G	T	1.16(0.92, 1.46)	0.214	0.964	G	T	1.12(1.01, 1.25)	0.033	0.720
rs495139	*TYMS*	G	C	0.90(0.76, 1.06)	0.216	0.964	C	G	0.98(0.91, 1.05)	0.493	0.963
rs1050152	*SLC22A4*	T	C	1.11(0.94, 1.32)	0.217	0.964	T	C	0.88(0.81, 0.95)	0.001	0.170
rs315984	*SLC22A2*	C	T	1.13(0.93, 1.37)	0.217	0.964	T	C	1.01(0.92, 1.11)	0.781	0.979
rs3016432	*FOLR1*	G	A	1.11(0.94, 1.31)	0.218	0.964	T	C	0.98(0.90, 1.07)	0.675	0.971
rs2450282	*SLC5A7*	A	G	0.79(0.54, 1.15)	0.220	0.964	C	T	0.99(0.83, 1.19)	0.944	0.986
rs8142477	*CHKB*	C	G	0.87(0.69, 1.09)	0.221	0.964	C	G	1.08(0.96, 1.22)	0.205	0.892
rs1021737	*CTH*	T	G	0.89(0.74, 1.07)	0.222	0.964	T	G	0.96(0.88, 1.04)	0.337	0.943
rs41385949	*SLC44A5*	A	G	0.79(0.53, 1.16)	0.222	0.964	T	C	1.13(0.93, 1.36)	0.216	0.892
rs10078190	*DHFR*	T	C	1.19(0.90, 1.59)	0.224	0.964	T	C	1.05(0.91, 1.20)	0.536	0.969
rs4694666	*MTHFD2L*	C	T	1.21(0.89, 1.63)	0.225	0.964	T	C	1.02(0.86, 1.21)	0.854	0.979
rs10179904	*MAT2A*	A	G	1.17(0.91, 1.51)	0.225	0.964	A	G	1.04(0.92, 1.18)	0.496	0.963
rs1023159	*SLC19A1*	A	G	0.90(0.76, 1.07)	0.226	0.964	A	G	1.05(0.96, 1.15)	0.315	0.928
rs11746555	*SLC22A5*	A	G	1.11(0.94, 1.32)	0.226	0.964	A	G	0.88(0.82, 0.96)	0.002	0.269
rs803454	*MTHFD1L*	A	G	0.83(0.61, 1.13)	0.229	0.964	--	--	--	--	--
rs10489810	*SLC44A3*	T	A	0.90(0.75, 1.07)	0.230	0.964	T	A	1.12(1.03, 1.22)	0.007	0.441
rs652888	*SLC44A4*	C	T	0.88(0.71, 1.09)	0.231	0.964	G	A	0.92(0.82, 1.03)	0.151	0.839
rs4120874	*MTR*	G	A	0.88(0.70, 1.09)	0.232	0.964	G	A	0.97(0.88, 1.08)	0.605	0.969
rs4894499	*PLD1*	C	T	0.88(0.72, 1.08)	0.235	0.964	C	T	0.94(0.85, 1.03)	0.197	0.892
rs1980983	*FTCD*	G	A	0.90(0.75, 1.07)	0.235	0.964	G	A	0.98(0.89, 1.07)	0.584	0.969
rs12438477	*MTHFS*	A	C	0.90(0.77, 1.07)	0.239	0.964	A	C	1.03(0.95, 1.12)	0.494	0.963
rs11951068	*DMGDH*	A	G	1.19(0.89, 1.58)	0.240	0.964	A	G	0.91(0.78, 1.06)	0.217	0.892
rs12912711	*MTHFS*	A	G	1.19(0.89, 1.58)	0.242	0.964	A	G	1.15(1.00, 1.31)	0.043	0.823
rs2243393	*CEPT1*	T	C	0.90(0.76, 1.07)	0.242	0.964	A	G	1.04(0.96, 1.12)	0.394	0.948
rs596881	*SLC22A2*	A	G	0.86(0.66, 1.11)	0.242	0.964	C	T	0.94(0.82, 1.07)	0.336	0.943
rs1047665	*MTHFD1L*	G	A	1.23(0.87, 1.72)	0.242	0.964	G	A	1.04(0.89, 1.22)	0.603	0.969
rs2299644	*FOLH1*	T	C	0.85(0.65, 1.12)	0.245	0.964	A	G	0.99(0.86, 1.13)	0.887	0.979
rs12401888	*SLC44A5*	T	C	1.16(0.90, 1.50)	0.245	0.964	T	C	1.03(0.92, 1.16)	0.578	0.969

RR: Risk Ratio; **CI**: Confidence Interval; **OR**: Odds Ratio; --: Unavailable in replication study

		NENA					CHOP				
SNP	Gene	Minor Allele	Major Allele	RR 95%(CI)	P-value	FDR Q-value	Minor Allele	Major Allele	OR 95%(CI)	P-value	FDR Q-value
rs6693082	*CTH*	G	T	0.90(0.74, 1.08)	0.245	0.964	G	T	0.95(0.87, 1.03)	0.203	0.892
rs4563403	*CHDH*	T	C	0.87(0.68, 1.10)	0.247	0.964	T	C	1.16(1.02, 1.32)	0.020	0.559
rs10489586	*SLC44A5*	A	G	0.78(0.51, 1.19)	0.247	0.964	A	G	1.00(0.81, 1.22)	0.971	0.995
rs2236484	*SLC19A1*	A	G	0.91(0.76, 1.07)	0.248	0.964	A	G	1.01(0.93, 1.10)	0.746	0.979
rs2880456	*MAT1A*	T	G	0.85(0.64, 1.12)	0.248	0.964	T	G	1.06(0.93, 1.22)	0.389	0.948
rs3795823	*CEPT1*	T	C	1.12(0.93, 1.35)	0.251	0.964	A	G	1.03(0.94, 1.13)	0.479	0.963
rs4817575	*GART*	A	G	0.86(0.66, 1.11)	0.251	0.964	A	G	1.02(0.90, 1.16)	0.703	0.977
rs1249839	*SLC44A5*	T	C	1.11(0.93, 1.32)	0.253	0.964	G	A	1.05(0.97, 1.13)	0.269	0.905
rs7586969	*ATIC*	G	A	0.91(0.77, 1.07)	0.256	0.964	A	G	1.06(0.98, 1.15)	0.133	0.839
rs11654690	*PLD2*	A	G	0.84(0.61, 1.14)	0.257	0.964	A	G	1.05(0.91, 1.21)	0.513	0.965
rs2484459	*CEPT1*	C	G	0.89(0.72, 1.09)	0.257	0.964	C	G	1.07(0.97, 1.19)	0.190	0.885
rs2797853	*SARDH*	A	G	0.90(0.76, 1.08)	0.257	0.964	--	--	--	--	--
rs13214952	*MTHFD1L*	G	T	0.90(0.75, 1.08)	0.258	0.964	T	G	1.04(0.96, 1.14)	0.348	0.943
rs2431332	*DMGDH*	G	A	0.89(0.73, 1.09)	0.258	0.964	G	A	1.00(0.92, 1.10)	0.924	0.983
rs4818789	*SLC19A1*	G	T	0.90(0.74, 1.08)	0.258	0.964	T	G	1.02(0.92, 1.14)	0.682	0.971
rs9290428	*PLD1*	G	C	0.91(0.77, 1.07)	0.260	0.964	G	C	0.94(0.87, 1.02)	0.116	0.837
rs4646755	*ALDH1L1*	C	A	0.90(0.74, 1.09)	0.261	0.964	G	T	0.96(0.88, 1.05)	0.419	0.959
rs3886314	*SLC44A3*	A	C	1.10(0.93, 1.31)	0.262	0.964	C	A	1.01(0.93, 1.10)	0.802	0.979
rs631305	*BHMT*	A	G	0.88(0.70, 1.10)	0.263	0.964	C	T	0.98(0.88, 1.09)	0.725	0.979
rs6721036	*SLC5A7*	T	C	0.86(0.66, 1.12)	0.263	0.964	C	T	1.05(0.93, 1.19)	0.401	0.949
rs4245407	*FOLR3*	A	G	1.10(0.93, 1.29)	0.264	0.964	A	G	1.00(0.93, 1.08)	0.996	0.998
rs8076949	*SLC46A1*	T	C	1.18(0.88, 1.56)	0.265	0.964	T	C	0.96(0.84, 1.09)	0.504	0.965
rs6479643	*SARDH*	C	G	0.91(0.77, 1.08)	0.266	0.964	--	--	--	--	--
rs333231	*SLC5A7*	A	G	1.11(0.92, 1.34)	0.268	0.964	A	G	1.08(0.99, 1.19)	0.090	0.831
rs4687747	*CHDH*	T	G	1.18(0.88, 1.59)	0.268	0.964	T	G	1.15(0.97, 1.35)	0.102	0.831
rs12201472	*MTHFD1L*	T	C	1.17(0.89, 1.55)	0.269	0.964	T	C	1.02(0.90, 1.17)	0.740	0.979
rs12636371	*ALDH1L1*	A	G	0.91(0.77, 1.08)	0.269	0.964	--	--	--	--	--
rs12210887	*SLC44A4*	T	G	0.82(0.58, 1.16)	0.270	0.964	T	G	1.05(0.89, 1.24)	0.578	0.969
rs7550014	*SLC44A3*	T	C	0.88(0.71, 1.10)	0.272	0.964	T	C	0.91(0.82, 1.02)	0.100	0.831
rs1557502	*CHKB*	A	G	0.89(0.73, 1.09)	0.272	0.964	T	C	1.04(0.94, 1.15)	0.430	0.962
rs7237052	*TYMS*	A	C	1.10(0.93, 1.30)	0.272	0.964	--	--	--	--	--
rs6766988	*CHDH*	A	T	0.86(0.66, 1.13)	0.272	0.964	A	T	1.05(0.91, 1.21)	0.527	0.969
rs36027301	*CHKA*	T	C	0.81(0.55, 1.18)	0.273	0.964	T	C	1.02(0.85, 1.22)	0.841	0.979
rs2373929	*NOS3*	T	C	1.09(0.93, 1.29)	0.275	0.964	A	G	1.04(0.96, 1.12)	0.350	0.943
rs13060596	*ALDH1L1*	T	G	0.91(0.76, 1.08)	0.277	0.964	--	--	--	--	--

RR: Risk Ratio; **CI**: Confidence Interval; **OR**: Odds Ratio; --: Unavailable in replication study

		NENA					CHOP				
SNP	Gene	Minor Allele	Major Allele	RR 95%(CI)	P-value	FDR Q-value	Minor Allele	Major Allele	OR 95%(CI)	P-value	FDR Q-value
rs7596024	*DNMT3A*	A	G	1.10(0.93, 1.30)	0.280	0.964	G	A	1.12(1.03, 1.21)	0.006	0.439
rs2288350	*DNMT1*	T	C	0.85(0.63, 1.14)	0.280	0.964	T	C	1.05(0.90, 1.24)	0.510	0.965
rs3119309	*SLC22A2*	T	C	1.16(0.89, 1.51)	0.281	0.964	T	C	1.03(0.92, 1.16)	0.591	0.969
rs140515	*CHKB*	C	G	0.91(0.77, 1.08)	0.281	0.964	--	--	--	--	--
rs13401241	*DNMT3A*	C	A	1.09(0.93, 1.29)	0.282	0.964	A	C	1.07(0.99, 1.16)	0.085	0.831
rs6546045	*DNMT3A*	C	T	1.10(0.92, 1.32)	0.282	0.964	T	C	1.08(0.99, 1.17)	0.075	0.831
rs2295084	*MTHFD1L*	A	G	1.13(0.90, 1.43)	0.285	0.964	T	C	0.99(0.88, 1.11)	0.823	0.979
rs4256166	*PLD1*	T	C	0.90(0.75, 1.09)	0.285	0.964	T	C	0.94(0.86, 1.03)	0.185	0.875
rs3120976	*MAT1A*	C	A	0.91(0.76, 1.08)	0.287	0.964	A	C	1.03(0.95, 1.12)	0.514	0.965
rs836788	*DHFR*	A	G	0.91(0.77, 1.08)	0.288	0.964	T	C	1.03(0.95, 1.12)	0.449	0.962
rs6141803	*DNMT3B*	C	T	1.12(0.91, 1.40)	0.288	0.964	C	T	1.05(0.94, 1.16)	0.381	0.948
rs316033	*SLC22A2*	G	A	1.10(0.92, 1.31)	0.288	0.964	G	A	0.94(0.87, 1.02)	0.149	0.839
rs129883	*SARDH*	G	C	1.10(0.92, 1.32)	0.289	0.964	--	--	--	--	--
rs7717	*FTCD*	C	G	1.13(0.90, 1.43)	0.289	0.964	C	G	0.95(0.85, 1.06)	0.359	0.948
rs9870993	*ALDH1L1*	T	G	1.10(0.92, 1.30)	0.290	0.964	--	--	--	--	--
rs10204232	*ATIC*	A	C	1.18(0.86, 1.61)	0.295	0.964	C	A	1.03(0.89, 1.20)	0.691	0.973
rs9267658	*SLC44A4*	T	C	1.14(0.89, 1.47)	0.297	0.964	C	T	1.01(0.89, 1.15)	0.898	0.979
rs1889036	*SLC44A5*	G	T	1.10(0.92, 1.33)	0.299	0.964	G	T	0.94(0.86, 1.02)	0.140	0.839
rs10380	*MTRR*	T	C	1.15(0.89, 1.48)	0.299	0.964	T	C	0.82(0.72, 0.94)	0.004	0.339
rs4147779	*CHKA*	G	A	0.90(0.75, 1.09)	0.300	0.964	A	G	1.01(0.92, 1.12)	0.784	0.979
rs4847362	*SLC44A3*	A	G	0.91(0.76, 1.09)	0.301	0.964	A	G	0.99(0.91, 1.08)	0.808	0.979
rs6495449	*MTHFS*	A	G	0.87(0.66, 1.14)	0.301	0.964	A	G	1.07(0.94, 1.22)	0.313	0.928
rs893363	*CHDH*	C	T	1.09(0.92, 1.30)	0.302	0.964	A	G	1.00(0.92, 1.08)	0.981	0.997
rs6760069	*ATIC*	A	G	0.88(0.70, 1.12)	0.302	0.964	A	G	1.02(0.91, 1.14)	0.720	0.979
rs11754661	*MTHFD1L*	A	G	0.84(0.59, 1.18)	0.304	0.964	A	G	1.04(0.90, 1.22)	0.575	0.969
rs35592604	*SLC44A5*	T	C	1.12(0.90, 1.40)	0.309	0.964	T	C	1.02(0.91, 1.15)	0.683	0.971
rs333214	*SLC5A7*	C	T	1.13(0.89, 1.43)	0.311	0.964	G	A	0.89(0.79, 1.00)	0.060	0.831
rs668641	*MTHFS*	A	G	1.09(0.92, 1.28)	0.311	0.964	T	C	1.01(0.94, 1.10)	0.740	0.979
rs1044988	*PCYT1A*	C	T	1.11(0.91, 1.36)	0.311	0.964	G	A	0.95(0.86, 1.04)	0.278	0.909
rs1405312	*SLC44A5*	T	C	1.13(0.89, 1.42)	0.312	0.964	A	G	0.99(0.89, 1.10)	0.838	0.979
rs336520	*DMGDH*	A	G	1.13(0.89, 1.44)	0.315	0.964	T	C	0.95(0.84, 1.08)	0.454	0.962
rs2586183	*MTHFS*	T	A	0.92(0.78, 1.08)	0.316	0.964	T	A	0.98(0.91, 1.06)	0.622	0.969
rs3806531	*SLC5A7*	G	A	1.09(0.92, 1.29)	0.316	0.964	C	T	1.02(0.94, 1.10)	0.672	0.971
rs8065874	*SHMT1*	T	C	0.91(0.75, 1.10)	0.318	0.964	T	C	1.07(0.97, 1.17)	0.161	0.854
rs4120852	*MAT1A*	C	A	0.92(0.77, 1.09)	0.319	0.964	T	G	1.04(0.96, 1.12)	0.378	0.948

RR: Risk Ratio; **CI**: Confidence Interval; **OR**: Odds Ratio; --: Unavailable in replication study

		NENA					CHOP				
SNP	Gene	Minor Allele	Major Allele	RR 95%(CI)	P-value	FDR Q-value	Minor Allele	Major Allele	OR 95%(CI)	P-value	FDR Q-value
rs4646748	*ALDH1L1*	T	C	1.11(0.90, 1.36)	0.320	0.964	A	G	0.97(0.88, 1.06)	0.487	0.963
rs2834233	*GART*	G	A	1.15(0.87, 1.52)	0.320	0.964	G	A	1.13(0.99, 1.28)	0.076	0.831
rs234785	*CBS*	G	C	0.92(0.77, 1.09)	0.323	0.964	G	C	0.99(0.90, 1.10)	0.872	0.979
rs1801394	*MTRR*	A	G	1.09(0.92, 1.29)	0.324	0.964	G	A	1.05(0.98, 1.14)	0.181	0.875
rs2077523	*ALDH1L1*	G	T	0.92(0.78, 1.09)	0.325	0.964	--	--	--	--	--
rs3797535	*DMGDH*	T	C	1.17(0.86, 1.60)	0.326	0.964	T	C	1.05(0.90, 1.22)	0.544	0.969
rs7937515	*FOLR3*	G	A	1.19(0.84, 1.69)	0.327	0.964	G	A	1.01(0.86, 1.18)	0.918	0.983
rs11849530	*MTHFD1*	G	A	0.91(0.75, 1.10)	0.327	0.964	G	A	1.03(0.93, 1.13)	0.604	0.969
rs12209517	*SLC22A3*	G	C	1.14(0.87, 1.49)	0.329	0.964	G	C	1.01(0.89, 1.14)	0.895	0.979
rs9897362	*PEMT*	A	G	0.84(0.60, 1.19)	0.329	0.964	A	G	1.01(0.86, 1.19)	0.900	0.979
rs2305795	*DNMT1*	G	A	0.92(0.78, 1.09)	0.331	0.964	A	G	0.97(0.90, 1.05)	0.464	0.963
rs556808	*MTHFD2L*	C	T	0.85(0.61, 1.18)	0.332	0.964	G	A	1.05(0.90, 1.23)	0.512	0.965
rs9383858	*MTHFD1L*	C	T	1.09(0.92, 1.29)	0.335	0.964	C	T	1.01(0.93, 1.10)	0.824	0.979
rs2236224	*MTHFD1*	T	C	1.09(0.92, 1.29)	0.338	0.964	A	G	1.04(0.96, 1.13)	0.306	0.927
rs12723350	*CTH*	C	T	1.19(0.83, 1.70)	0.338	0.964	C	T	1.02(0.88, 1.18)	0.776	0.979
rs10514154	*DMGDH*	G	A	0.90(0.73, 1.11)	0.339	0.964	G	A	0.93(0.84, 1.02)	0.134	0.839
rs12366105	*FOLR3*	C	T	1.08(0.92, 1.28)	0.341	0.964	C	T	1.02(0.94, 1.10)	0.673	0.971
rs9478934	*MTHFD1L*	G	A	1.19(0.83, 1.69)	0.342	0.964	G	A	1.01(0.86, 1.19)	0.881	0.979
rs859101	*SLC44A3*	A	C	1.08(0.92, 1.28)	0.342	0.964	T	G	0.94(0.86, 1.01)	0.095	0.831
rs2445887	*DMGDH*	T	C	0.92(0.78, 1.09)	0.343	0.964	A	G	0.98(0.90, 1.06)	0.634	0.969
rs1109859	*PEMT*	C	T	0.90(0.73, 1.12)	0.343	0.964	A	G	0.96(0.86, 1.07)	0.445	0.962
rs2286671	*PLD2*	C	T	1.09(0.92, 1.29)	0.344	0.964	A	G	1.04(0.96, 1.13)	0.294	0.915
rs129956	*SARDH*	C	T	0.85(0.61, 1.19)	0.344	0.964	--	--	--	--	--
rs3744962	*TYMS*	C	T	1.15(0.86, 1.54)	0.346	0.964	G	A	1.12(1.03, 1.23)	0.010	0.467
rs17080689	*MTHFD1L*	C	A	0.88(0.67, 1.15)	0.347	0.964	C	A	1.00(0.88, 1.14)	0.988	0.998
rs4744533	*SARDH*	T	C	0.92(0.78, 1.09)	0.347	0.964	--	--	--	--	--
rs3796349	*CHDH*	G	A	0.86(0.62, 1.18)	0.347	0.964	G	A	1.25(1.05, 1.50)	0.014	0.518
rs12906758	*MTHFS*	A	T	1.11(0.90, 1.37)	0.348	0.964	A	T	1.05(0.95, 1.16)	0.339	0.943
rs4676168	*SLC5A7*	T	C	0.92(0.77, 1.10)	0.348	0.964	T	C	0.98(0.91, 1.07)	0.693	0.973
rs131778	*CHKB*	T	C	0.93(0.79, 1.09)	0.349	0.964	--	--	--	--	--
rs3818239	*MTHFD1*	G	A	0.88(0.68, 1.15)	0.349	0.964	C	T	0.90(0.79, 1.02)	0.086	0.831
rs11634787	*MTHFS*	A	G	0.86(0.63, 1.18)	0.349	0.964	A	G	1.05(0.91, 1.20)	0.528	0.969
rs316025	*SLC22A2*	A	G	1.10(0.90, 1.33)	0.353	0.964	C	T	0.97(0.89, 1.06)	0.490	0.963
rs6774437	*ALDH1L1*	C	A	0.93(0.79, 1.09)	0.353	0.964	--	--	--	--	--
rs6087988	*DNMT3B*	T	C	1.09(0.91, 1.32)	0.353	0.964	T	C	0.97(0.89, 1.07)	0.578	0.969

RR: Risk Ratio; **CI**: Confidence Interval; **OR**: Odds Ratio; --: Unavailable in replication study

		NENA					CHOP				
SNP	Gene	Minor Allele	Major Allele	RR 95%(CI)	P-value	FDR Q-value	Minor Allele	Major Allele	OR 95%(CI)	P-value	FDR Q-value
rs17597141	*CHKA*	C	G	0.91(0.74, 1.12)	0.353	0.964	C	G	1.04(0.92, 1.17)	0.577	0.969
rs2481030	*SLC22A3*	G	A	0.92(0.77, 1.10)	0.355	0.964	G	A	1.00(0.92, 1.08)	0.906	0.979
rs12638724	*ALDH1L1*	A	G	0.93(0.79, 1.09)	0.359	0.964	--	--	--	--	--
rs1800779	*NOS3*	G	A	0.92(0.78, 1.09)	0.360	0.964	A	G	1.02(0.94, 1.10)	0.664	0.971
rs7236459	*TYMS*	G	A	1.14(0.86, 1.50)	0.360	0.964	G	A	1.12(0.94, 1.33)	0.199	0.892
rs9889584	*PEMT*	A	G	0.86(0.62, 1.19)	0.361	0.964	A	G	1.01(0.86, 1.19)	0.871	0.979
rs6669849	*SLC44A3*	T	C	1.20(0.81, 1.80)	0.365	0.964	--	--	--	--	--
rs1256146	*MTHFD1*	A	G	1.10(0.90, 1.34)	0.366	0.964	A	G	1.01(0.92, 1.12)	0.793	0.979
rs17824591	*MTHFD1*	A	G	0.91(0.74, 1.12)	0.367	0.964	A	G	1.03(0.93, 1.15)	0.558	0.969
rs6910091	*MTHFD1L*	G	T	1.09(0.90, 1.31)	0.369	0.964	G	T	1.05(0.96, 1.14)	0.315	0.928
rs696620	*SLC44A3*	C	T	1.08(0.92, 1.27)	0.369	0.964	G	A	0.99(0.92, 1.07)	0.853	0.979
rs17080776	*MTHFD1L*	C	T	1.08(0.91, 1.28)	0.370	0.964	C	T	0.99(0.92, 1.08)	0.860	0.979
rs10493570	*SLC44A5*	T	C	1.12(0.87, 1.43)	0.374	0.964	T	C	1.04(0.93, 1.17)	0.501	0.963
rs859063	*SLC44A3*	A	G	0.93(0.78, 1.10)	0.374	0.964	G	A	1.02(0.94, 1.11)	0.626	0.969
rs567754	*BHMT*	T	C	1.09(0.91, 1.30)	0.375	0.964	T	C	1.00(0.92, 1.09)	0.969	0.995
rs6792030	*ALDH1L1*	C	T	1.10(0.89, 1.36)	0.375	0.964	--	--	--	--	--
rs6745054	*MTHFD2*	C	T	0.90(0.72, 1.13)	0.376	0.964	C	T	0.94(0.83, 1.06)	0.289	0.909
rs3774609	*CHDH*	G	T	0.93(0.79, 1.09)	0.376	0.964	G	T	1.02(0.94, 1.11)	0.589	0.969
rs4920035	*CBS*	A	G	0.89(0.68, 1.16)	0.377	0.964	G	A	0.91(0.80, 1.03)	0.131	0.839
rs11627387	*MTHFD1*	A	G	0.92(0.77, 1.10)	0.377	0.964	A	G	0.95(0.87, 1.03)	0.237	0.901
rs9383551	*MTHFD1L*	C	T	1.16(0.84, 1.60)	0.379	0.964	C	T	1.01(0.85, 1.20)	0.907	0.979
rs129940	*SARDH*	G	A	0.86(0.61, 1.21)	0.382	0.964	--	--	--	--	--
rs316002	*SLC22A2*	T	C	0.90(0.72, 1.14)	0.387	0.964	T	C	1.00(0.89, 1.13)	0.994	0.998
rs161871	*MTRR*	G	A	1.09(0.89, 1.34)	0.388	0.964	G	A	0.92(0.83, 1.02)	0.124	0.838
rs11755633	*MTHFD1L*	G	A	1.11(0.87, 1.42)	0.392	0.964	G	A	0.92(0.81, 1.03)	0.148	0.839
rs2838951	*SLC19A1*	G	C	1.08(0.91, 1.27)	0.394	0.964	C	G	1.01(0.93, 1.09)	0.814	0.979
rs131749	*CHKB*	A	G	0.93(0.78, 1.10)	0.395	0.964	C	T	0.95(0.87, 1.03)	0.224	0.892
rs11235451	*FOLR3*	A	T	1.08(0.91, 1.28)	0.396	0.964	A	T	1.02(0.94, 1.10)	0.681	0.971
rs6919680	*MTHFD1L*	G	T	1.13(0.85, 1.49)	0.396	0.964	G	T	0.86(0.73, 1.00)	0.056	0.831
rs10819309	*FPGS*	A	G	0.93(0.78, 1.10)	0.398	0.964	G	A	1.02(0.94, 1.11)	0.564	0.969
rs3851059	*MAT1A*	A	G	0.93(0.77, 1.11)	0.400	0.964	A	G	1.00(0.91, 1.08)	0.910	0.979
rs957903	*SLC44A1*	C	T	1.08(0.90, 1.31)	0.401	0.964	G	A	1.02(0.93, 1.11)	0.661	0.971
rs17677908	*MAT1A*	G	A	0.90(0.70, 1.15)	0.403	0.964	G	A	0.99(0.88, 1.12)	0.845	0.979
rs10195701	*SLC5A7*	C	T	1.10(0.88, 1.37)	0.404	0.964	C	T	0.91(0.82, 1.01)	0.088	0.831
rs7763414	*MTHFD1L*	T	A	1.10(0.88, 1.38)	0.405	0.964	T	A	1.01(0.91, 1.13)	0.793	0.979

RR: Risk Ratio; **CI**: Confidence Interval; **OR**: Odds Ratio; --: Unavailable in replication study

		NENA					CHOP				
SNP	Gene	Minor Allele	Major Allele	RR 95%(CI)	P-value	FDR Q-value	Minor Allele	Major Allele	OR 95%(CI)	P-value	FDR Q-value
rs3972	*CBS*	T	C	1.11(0.87, 1.41)	0.405	0.964	T	C	1.08(0.96, 1.21)	0.206	0.892
rs17232682	*MTHFD2L*	C	T	0.90(0.71, 1.15)	0.406	0.964	C	T	0.99(0.88, 1.11)	0.843	0.979
rs2071010	*FOLR1*	A	G	0.88(0.64, 1.20)	0.413	0.964	A	G	1.02(0.86, 1.20)	0.841	0.979
rs4702506	*MTRR*	C	T	1.09(0.88, 1.36)	0.414	0.964	C	T	1.12(1.01, 1.24)	0.028	0.689
rs3821466	*ALDH1L1*	T	C	0.93(0.78, 1.11)	0.416	0.964	A	G	0.91(0.84, 0.99)	0.028	0.689
rs12999687	*DNMT3A*	T	G	1.07(0.91, 1.26)	0.418	0.964	G	T	1.10(1.01, 1.19)	0.020	0.559
rs4244599	*PEMT*	G	A	0.93(0.79, 1.10)	0.419	0.964	C	T	0.98(0.91, 1.07)	0.705	0.977
rs16853723	*ATIC*	C	T	0.91(0.71, 1.15)	0.420	0.964	C	T	1.02(0.91, 1.15)	0.679	0.971
rs9975829	*GART*	G	A	1.07(0.90, 1.27)	0.420	0.964	G	A	1.07(0.99, 1.17)	0.088	0.831
rs12987326	*DNMT3A*	G	A	1.07(0.91, 1.27)	0.421	0.964	A	G	1.12(1.03, 1.21)	0.006	0.439
rs2177268	*AMT*	A	T	1.08(0.90, 1.30)	0.422	0.964	T	A	1.02(0.94, 1.12)	0.617	0.969
rs4817579	*GART*	T	C	1.07(0.90, 1.28)	0.424	0.964	C	T	1.02(0.94, 1.11)	0.575	0.969
rs4819130	*SLC19A1*	C	T	0.93(0.79, 1.10)	0.424	0.964	T	C	1.01(0.93, 1.09)	0.877	0.979
rs2073643	*SLC22A5*	T	C	0.93(0.79, 1.10)	0.425	0.964	C	T	0.93(0.86, 1.01)	0.089	0.831
rs2847607	*TYMS*	A	G	1.08(0.89, 1.32)	0.425	0.964	T	C	1.01(0.93, 1.10)	0.732	0.979
rs10874311	*SLC44A5*	T	C	1.08(0.90, 1.29)	0.426	0.964	T	C	0.93(0.85, 1.01)	0.078	0.831
rs2987981	*MTHFD1*	C	T	0.93(0.76, 1.12)	0.428	0.964	G	A	1.04(0.96, 1.14)	0.341	0.943
rs487637	*MTHFD1L*	G	T	1.08(0.90, 1.29)	0.433	0.964	A	C	1.01(0.92, 1.09)	0.907	0.979
rs316020	*SLC22A2*	T	C	0.90(0.69, 1.17)	0.438	0.964	G	A	0.97(0.85, 1.10)	0.615	0.969
rs2510234	*SARDH*	C	T	1.07(0.90, 1.27)	0.440	0.964	--	--	--	--	--
rs694821	*SARDH*	G	A	1.06(0.91, 1.25)	0.440	0.964	--	--	--	--	--
rs3783731	*MTHFD1*	T	C	1.09(0.88, 1.35)	0.440	0.964	A	G	1.03(0.93, 1.14)	0.601	0.969
rs4902278	*MTHFD1*	A	G	0.87(0.60, 1.25)	0.442	0.964	G	A	1.14(0.96, 1.36)	0.145	0.839
rs617219	*BHMT*	C	A	1.07(0.90, 1.27)	0.445	0.964	C	A	1.01(0.93, 1.10)	0.818	0.979
rs734693	*DNMT3A*	C	T	0.93(0.78, 1.12)	0.446	0.964	T	C	0.99(0.91, 1.08)	0.831	0.979
rs9322301	*MTHFD1L*	C	T	1.07(0.90, 1.26)	0.447	0.964	C	T	1.02(0.94, 1.10)	0.667	0.971
rs12652027	*MAT2B*	C	T	1.16(0.79, 1.71)	0.449	0.964	C	T	1.18(0.97, 1.42)	0.097	0.831
rs10987742	*FPGS*	T	C	0.92(0.75, 1.14)	0.451	0.964	T	C	1.04(0.94, 1.15)	0.431	0.962
rs2073064	*MTHFD1L*	G	A	0.92(0.73, 1.15)	0.451	0.964	C	T	1.08(0.94, 1.22)	0.274	0.905
rs2163005	*MTHFS*	G	A	1.07(0.90, 1.26)	0.452	0.964	C	T	1.06(0.98, 1.15)	0.139	0.839
rs9397032	*MTHFD1L*	T	G	0.94(0.80, 1.11)	0.454	0.964	G	T	1.02(0.94, 1.10)	0.621	0.969
rs2076828	*SLC22A3*	G	C	0.94(0.80, 1.11)	0.457	0.964	G	C	1.04(0.97, 1.13)	0.279	0.909
rs9869368	*PLD1*	G	A	1.09(0.86, 1.38)	0.457	0.964	G	A	0.98(0.88, 1.10)	0.734	0.979
rs17102596	*MAT1A*	C	T	0.92(0.75, 1.14)	0.459	0.964	C	T	0.97(0.87, 1.07)	0.515	0.965
rs7544408	*SLC44A5*	C	G	0.94(0.79, 1.11)	0.459	0.964	G	C	0.94(0.87, 1.02)	0.153	0.839

RR: Risk Ratio; **CI**: Confidence Interval; **OR**: Odds Ratio; --: Unavailable in replication study

		NENA					CHOP				
SNP	Gene	Minor Allele	Major Allele	RR 95%(CI)	P-value	FDR Q-value	Minor Allele	Major Allele	OR 95%(CI)	P-value	FDR Q-value
rs17269265	*SLC5A7*	G	A	1.08(0.88, 1.33)	0.459	0.964	G	A	1.09(1.00, 1.20)	0.051	0.823
rs17823744	*DMGDH*	G	A	1.11(0.85, 1.44)	0.460	0.964	G	A	1.02(0.90, 1.15)	0.771	0.979
rs1476413	*MTHFR*	A	G	1.08(0.89, 1.31)	0.460	0.964	T	C	1.01(0.92, 1.10)	0.824	0.979
rs12995245	*DNMT3A*	C	T	1.06(0.90, 1.25)	0.460	0.964	T	C	1.11(1.03, 1.20)	0.009	0.446
rs1045020	*SLC22A5*	T	C	1.10(0.85, 1.44)	0.461	0.964	T	C	1.04(0.92, 1.19)	0.522	0.967
rs555671	*CTH*	T	C	0.88(0.63, 1.24)	0.461	0.964	A	G	1.11(0.93, 1.31)	0.252	0.902
rs17622208	*SLC22A5*	A	G	1.07(0.90, 1.26)	0.464	0.964	A	G	0.86(0.79, 0.93)	0.000	0.074
rs523230	*TYMS*	C	T	1.07(0.89, 1.28)	0.470	0.964	A	G	1.09(1.00, 1.20)	0.045	0.823
rs1051266	*SLC19A1*	A	G	0.94(0.79, 1.11)	0.470	0.964	C	T	1.00(0.93, 1.09)	0.923	0.983
rs1788484	*CBS*	T	C	0.94(0.78, 1.12)	0.471	0.964	T	C	0.99(0.91, 1.08)	0.811	0.979
rs2618372	*DHFR*	A	C	1.07(0.89, 1.28)	0.471	0.964	A	C	0.99(0.91, 1.08)	0.835	0.979
rs624249	*SLC22A2*	A	C	0.94(0.79, 1.12)	0.472	0.964	A	C	1.04(0.95, 1.14)	0.384	0.948
rs7946	*PEMT*	C	T	1.07(0.89, 1.29)	0.472	0.964	T	C	0.99(0.91, 1.08)	0.862	0.979
rs4979631	*SARDH*	A	G	0.94(0.78, 1.12)	0.472	0.964	--	--	--	--	--
rs17535909	*MAT2B*	A	G	0.94(0.79, 1.12)	0.472	0.964	A	G	0.96(0.88, 1.05)	0.412	0.959
rs1643638	*DHFR*	C	T	1.07(0.89, 1.28)	0.473	0.964	C	T	0.99(0.91, 1.08)	0.833	0.979
rs9478908	*MTHFD1L*	G	A	0.93(0.77, 1.13)	0.473	0.964	G	A	1.06(0.96, 1.16)	0.237	0.901
rs10494126	*CEPT1*	A	C	1.10(0.85, 1.42)	0.474	0.964	A	C	0.98(0.87, 1.11)	0.764	0.979
rs273915	*SLC22A4*	C	G	0.94(0.78, 1.12)	0.474	0.964	C	G	0.95(0.87, 1.03)	0.215	0.892
rs859096	*SLC44A3*	C	A	0.94(0.78, 1.12)	0.474	0.964	T	G	1.03(0.95, 1.13)	0.446	0.962
rs12344130	*SLC44A1*	T	G	0.90(0.67, 1.21)	0.475	0.964	T	G	1.03(0.88, 1.20)	0.730	0.979
rs13306567	*MTHFR*	C	G	1.15(0.78, 1.69)	0.476	0.964	G	C	0.92(0.78, 1.10)	0.363	0.948
rs1643650	*DHFR*	C	T	1.07(0.89, 1.28)	0.476	0.964	C	T	0.99(0.91, 1.08)	0.841	0.979
rs1571511	*MTHFD1*	G	A	0.93(0.75, 1.14)	0.477	0.964	C	T	1.03(0.94, 1.13)	0.472	0.963
rs1051319	*CBS*	G	C	1.09(0.85, 1.41)	0.477	0.964	C	G	0.95(0.84, 1.07)	0.419	0.959
rs10484779	*MTHFD1L*	G	T	0.92(0.73, 1.16)	0.481	0.964	G	T	0.93(0.83, 1.04)	0.213	0.892
rs2072197	*TCN2*	A	C	0.92(0.73, 1.16)	0.481	0.964	C	A	1.01(0.90, 1.13)	0.898	0.979
rs12743566	*SLC44A5*	G	A	1.11(0.83, 1.50)	0.482	0.964	--	--	--	--	--
rs17184211	*MTRR*	T	A	0.93(0.76, 1.14)	0.483	0.964	T	A	0.96(0.87, 1.05)	0.364	0.948
rs538017	*MTHFD1L*	C	T	1.07(0.89, 1.28)	0.484	0.964	G	A	1.06(0.97, 1.17)	0.181	0.875
rs6860806	*SLC22A4*	A	G	0.94(0.80, 1.11)	0.484	0.964	G	A	0.92(0.85, 0.99)	0.030	0.689
rs4629694	*MTHFD1L*	C	T	1.19(0.73, 1.95)	0.486	0.964	C	T	0.88(0.69, 1.11)	0.271	0.905
rs3912161	*SLC22A2*	G	A	1.12(0.81, 1.56)	0.486	0.964	--	--	--	--	--
rs4820887	*TCN2*	A	G	0.91(0.69, 1.20)	0.488	0.964	A	G	0.95(0.83, 1.09)	0.439	0.962
rs647370	*FOLH1*	A	G	0.94(0.77, 1.13)	0.493	0.964	T	C	1.00(0.91, 1.10)	0.918	0.983

RR: Risk Ratio; **CI**: Confidence Interval; **OR**: Odds Ratio; --: Unavailable in replication study

		NENA					CHOP				
SNP	Gene	Minor Allele	Major Allele	RR 95%(CI)	P-value	FDR Q-value	Minor Allele	Major Allele	OR 95%(CI)	P-value	FDR Q-value
rs1256142	*MTHFD1*	C	T	1.06(0.90, 1.24)	0.493	0.964	A	G	1.00(0.92, 1.08)	0.926	0.983
rs10857859	*CEPT1*	C	G	1.06(0.89, 1.27)	0.495	0.964	C	G	1.08(1.00, 1.18)	0.064	0.831
rs3764897	*PLD2*	T	C	1.08(0.86, 1.35)	0.496	0.964	A	G	1.10(0.97, 1.25)	0.151	0.839
rs558936	*MTHFD1L*	A	G	0.94(0.78, 1.13)	0.496	0.964	C	T	0.95(0.87, 1.04)	0.291	0.911
rs11908960	*FTCD*	C	T	0.92(0.73, 1.17)	0.496	0.964	C	T	1.07(0.92, 1.23)	0.394	0.948
rs4846052	*MTHFR*	T	C	0.94(0.80, 1.12)	0.496	0.964	C	T	1.00(0.92, 1.08)	0.981	0.997
rs272894	*SLC22A4*	G	A	0.94(0.80, 1.12)	0.499	0.964	T	C	0.90(0.83, 0.97)	0.008	0.446
rs3849308	*SLC44A3*	G	A	0.94(0.79, 1.12)	0.500	0.964	C	T	0.93(0.85, 1.01)	0.076	0.831
rs17096504	*SLC44A5*	A	G	1.13(0.79, 1.64)	0.501	0.964	A	G	1.10(0.93, 1.32)	0.274	0.905
rs10854479	*FTCD*	C	T	0.94(0.78, 1.13)	0.502	0.964	T	C	0.99(0.90, 1.09)	0.856	0.979
rs16879258	*MTRR*	A	C	1.09(0.85, 1.39)	0.502	0.964	A	C	0.96(0.85, 1.07)	0.435	0.962
rs13161245	*DHFR*	G	A	1.06(0.89, 1.28)	0.503	0.964	G	A	0.99(0.91, 1.08)	0.861	0.979
rs1478834	*DHFR*	A	C	1.06(0.89, 1.28)	0.503	0.964	A	C	0.99(0.91, 1.08)	0.860	0.979
rs711352	*PEMT*	C	G	1.07(0.88, 1.29)	0.504	0.964	C	G	0.98(0.89, 1.07)	0.592	0.969
rs6087983	*DNMT3B*	T	G	1.08(0.87, 1.33)	0.506	0.964	T	G	0.99(0.89, 1.10)	0.798	0.979
rs7638797	*PCYT1A*	C	A	1.06(0.89, 1.25)	0.506	0.964	C	A	0.96(0.88, 1.05)	0.362	0.948
rs9432596	*SLC44A3*	A	G	1.07(0.87, 1.31)	0.507	0.964	A	G	0.96(0.87, 1.06)	0.376	0.948
rs11155773	*MTHFD1L*	A	G	0.94(0.78, 1.13)	0.507	0.964	A	G	0.94(0.86, 1.03)	0.196	0.892
rs729352	*MAT2B*	T	C	1.06(0.89, 1.28)	0.507	0.964	T	C	1.01(0.93, 1.11)	0.749	0.979
rs12121543	*MTHFR*	A	C	1.07(0.88, 1.30)	0.507	0.964	--	--	--	--	--
rs803422	*MTHFD1L*	T	C	1.06(0.88, 1.28)	0.507	0.964	G	A	1.01(0.93, 1.10)	0.741	0.979
rs327588	*MTRR*	C	G	1.08(0.87, 1.34)	0.508	0.964	G	C	0.95(0.86, 1.05)	0.350	0.943
rs7830	*NOS3*	A	C	1.06(0.89, 1.25)	0.509	0.964	T	G	1.03(0.94, 1.13)	0.537	0.969
rs274567	*SLC22A5*	A	G	0.95(0.80, 1.12)	0.511	0.964	T	C	1.11(1.02, 1.20)	0.015	0.531
rs1548362	*SARDH*	C	T	0.94(0.78, 1.13)	0.513	0.964	--	--	--	--	--
rs6672579	*SLC44A5*	A	G	1.06(0.90, 1.24)	0.514	0.964	A	G	1.03(0.95, 1.11)	0.436	0.962
rs9267649	*SLC44A4*	A	G	1.08(0.86, 1.35)	0.514	0.964	G	A	1.05(0.94, 1.18)	0.363	0.948
rs11235466	*FOLR2*	C	T	0.90(0.65, 1.24)	0.516	0.964	C	T	1.01(0.86, 1.18)	0.934	0.986
rs2847149	*TYMS*	A	G	1.05(0.90, 1.24)	0.516	0.964	A	G	0.94(0.88, 1.01)	0.074	0.831
rs13036246	*DNMT3A*	T	C	0.95(0.80, 1.12)	0.516	0.964	T	C	1.09(1.01, 1.18)	0.029	0.689
rs175862	*MTHFD1L*	C	T	1.06(0.88, 1.28)	0.516	0.964	A	G	1.05(0.96, 1.14)	0.310	0.927
rs2115540	*MTHFS*	T	C	0.95(0.80, 1.12)	0.519	0.964	G	A	1.05(0.97, 1.13)	0.229	0.892
rs737953	*TCN2*	G	C	0.95(0.80, 1.12)	0.520	0.964	--	--	--	--	--
rs582326	*SARDH*	G	C	1.06(0.89, 1.26)	0.522	0.964	--	--	--	--	--
rs11235441	*FOLR3*	A	G	0.87(0.56, 1.35)	0.522	0.964	A	G	0.88(0.66, 1.18)	0.400	0.949

RR: Risk Ratio; **CI**: Confidence Interval; **OR**: Odds Ratio; --: Unavailable in replication study

		NENA					CHOP				
SNP	Gene	Minor Allele	Major Allele	RR 95%(CI)	P-value	FDR Q-value	Minor Allele	Major Allele	OR 95%(CI)	P-value	FDR Q-value
rs416158	*PLD1*	A	T	0.93(0.74, 1.16)	0.522	0.964	T	A	0.98(0.87, 1.09)	0.684	0.971
rs7639712	*ALDH1L1*	G	A	0.93(0.73, 1.17)	0.522	0.964	--	--	--	--	--
rs1001761	*TYMS*	T	C	1.05(0.90, 1.24)	0.523	0.964	A	G	0.94(0.89, 1.01)	0.082	0.831
rs1476331	*PCYT1A*	G	A	1.05(0.90, 1.24)	0.524	0.964	C	T	0.94(0.86, 1.01)	0.102	0.831
rs2299648	*FOLH1*	A	G	1.06(0.89, 1.26)	0.524	0.964	C	T	1.02(0.93, 1.11)	0.730	0.979
rs9644967	*SLC44A1*	A	G	1.06(0.89, 1.25)	0.524	0.964	--	--	--	--	--
rs7712332	*DHFR*	G	A	1.06(0.89, 1.26)	0.525	0.964	G	A	0.98(0.90, 1.06)	0.562	0.969
rs2519154	*SARDH*	G	A	1.06(0.89, 1.25)	0.526	0.964	--	--	--	--	--
rs11880388	*DNMT1*	A	G	1.05(0.90, 1.24)	0.526	0.964	A	G	1.01(0.93, 1.09)	0.832	0.979
rs497161	*MTHFD1L*	A	G	0.95(0.80, 1.12)	0.527	0.964	T	C	1.07(0.98, 1.16)	0.113	0.837
rs162029	*MTRR*	A	G	1.07(0.87, 1.30)	0.527	0.964	A	G	0.96(0.86, 1.06)	0.385	0.948
rs2277820	*FTCD*	T	C	0.94(0.78, 1.13)	0.528	0.964	T	C	1.02(0.94, 1.11)	0.658	0.971
rs315996	*SLC22A2*	A	G	0.92(0.72, 1.18)	0.529	0.964	A	G	1.01(0.89, 1.15)	0.821	0.979
rs2241553	*CHPT1*	C	A	0.94(0.79, 1.13)	0.530	0.964	G	T	0.96(0.89, 1.05)	0.388	0.948
rs2297291	*SLC19A1*	A	G	0.95(0.80, 1.12)	0.531	0.964	G	A	1.02(0.94, 1.11)	0.591	0.969
rs3789699	*SLC44A3*	C	T	0.92(0.70, 1.20)	0.531	0.964	C	T	1.00(0.88, 1.13)	0.976	0.996
rs1868138	*ALDH1L1*	T	A	1.06(0.88, 1.29)	0.533	0.964	--	--	--	--	--
rs2502741	*SARDH*	G	A	0.95(0.81, 1.11)	0.533	0.964	--	--	--	--	--
rs7737937	*SLC22A4*	A	G	0.93(0.74, 1.17)	0.535	0.964	A	G	1.02(0.92, 1.14)	0.674	0.971
rs3087896	*PCYT1A*	T	C	1.08(0.84, 1.40)	0.535	0.964	A	G	0.91(0.81, 1.02)	0.116	0.837
rs3760183	*PEMT*	T	G	1.08(0.84, 1.40)	0.536	0.964	T	G	0.98(0.87, 1.11)	0.777	0.979
rs2073067	*MTHFD1L*	C	G	1.06(0.89, 1.26)	0.537	0.964	G	C	0.99(0.91, 1.07)	0.762	0.979
rs13306560	*MTHFR*	A	G	1.13(0.77, 1.66)	0.539	0.964	T	C	0.92(0.78, 1.09)	0.351	0.943
rs4646767	*ALDH1L1*	T	C	0.95(0.81, 1.12)	0.539	0.964	G	A	0.96(0.89, 1.04)	0.357	0.948
rs6502823	*PLD2*	T	C	0.91(0.67, 1.23)	0.539	0.964	T	C	1.00(0.86, 1.16)	0.998	0.998
rs162031	*MTRR*	T	C	1.07(0.86, 1.32)	0.540	0.964	C	T	0.96(0.87, 1.06)	0.447	0.962
rs2839947	*MTHFD1L*	C	T	1.05(0.89, 1.25)	0.540	0.964	C	T	0.99(0.91, 1.07)	0.724	0.979
rs3816556	*DNMT1*	C	G	0.94(0.79, 1.14)	0.541	0.964	C	G	1.09(0.98, 1.20)	0.111	0.837
rs12634587	*PCYT1A*	G	C	0.94(0.79, 1.13)	0.542	0.964	G	C	0.98(0.90, 1.07)	0.659	0.971
rs6902496	*MTHFD1L*	T	C	0.94(0.77, 1.15)	0.545	0.964	T	C	1.02(0.92, 1.12)	0.711	0.979
rs2275122	*CEPT1*	C	A	1.09(0.83, 1.42)	0.546	0.964	G	T	0.94(0.83, 1.07)	0.347	0.943
rs4646398	*PEMT*	G	C	1.10(0.80, 1.52)	0.546	0.964	C	G	1.02(0.87, 1.19)	0.825	0.979
rs2838950	*SLC19A1*	T	C	0.94(0.77, 1.15)	0.547	0.964	T	C	1.05(0.95, 1.15)	0.346	0.943
rs3850181	*PLD1*	A	G	1.10(0.81, 1.50)	0.550	0.964	A	G	1.06(0.89, 1.27)	0.522	0.967
rs2516557	*CHKB*	A	G	1.10(0.80, 1.51)	0.550	0.964	--	--	--	--	--

RR: Risk Ratio; **CI**: Confidence Interval; **OR**: Odds Ratio; --: Unavailable in replication study

		NENA					CHOP				
SNP	Gene	Minor Allele	Major Allele	RR 95%(CI)	P-value	FDR Q-value	Minor Allele	Major Allele	OR 95%(CI)	P-value	FDR Q-value
rs2073191	*MTHFD1L*	G	A	0.94(0.78, 1.14)	0.551	0.964	C	T	0.97(0.88, 1.06)	0.493	0.963
rs859106	*SLC44A3*	C	A	0.93(0.73, 1.19)	0.553	0.964	T	G	0.81(0.72, 0.91)	0.000	0.074
rs17097955	*SLC44A5*	C	T	1.11(0.79, 1.56)	0.553	0.964	C	T	1.04(0.88, 1.23)	0.627	0.969
rs7173671	*MTHFS*	A	G	0.95(0.80, 1.13)	0.553	0.964	A	G	1.00(0.92, 1.08)	0.989	0.998
rs3776455	*MTRR*	G	A	1.05(0.88, 1.26)	0.554	0.964	T	C	1.00(0.92, 1.09)	0.973	0.996
rs2236479	*SLC19A1*	A	G	1.05(0.89, 1.25)	0.555	0.964	A	G	1.03(0.94, 1.13)	0.478	0.963
rs4846049	*MTHFR*	T	G	1.06(0.88, 1.26)	0.555	0.964	G	T	1.01(0.93, 1.10)	0.851	0.979
rs17230459	*MTHFD2L*	T	C	1.07(0.86, 1.32)	0.556	0.964	T	C	0.92(0.82, 1.03)	0.134	0.839
rs2043305	*SLC44A2*	T	C	1.06(0.87, 1.30)	0.556	0.964	G	A	0.93(0.85, 1.03)	0.166	0.854
rs96525	*DMGDH*	T	C	0.94(0.76, 1.16)	0.558	0.964	T	C	1.03(0.93, 1.14)	0.604	0.969
rs1563632	*SHMT1*	C	T	0.95(0.79, 1.13)	0.558	0.964	A	G	0.99(0.92, 1.08)	0.882	0.979
rs10518120	*MTHFD2L*	G	A	1.07(0.86, 1.32)	0.561	0.964	G	A	1.02(0.92, 1.13)	0.726	0.979
rs2853532	*TYMS*	T	C	1.05(0.89, 1.25)	0.562	0.964	T	C	0.97(0.91, 1.03)	0.307	0.927
rs653753	*SLC22A2*	C	G	1.07(0.84, 1.37)	0.562	0.964	G	C	0.95(0.84, 1.08)	0.450	0.962
rs7177659	*MTHFS*	A	C	0.95(0.81, 1.12)	0.563	0.964	C	A	0.99(0.92, 1.08)	0.890	0.979
rs12122907	*SLC44A5*	A	G	1.06(0.86, 1.32)	0.564	0.964	A	G	1.04(0.94, 1.15)	0.455	0.962
rs4676169	*SLC5A7*	G	A	0.95(0.81, 1.13)	0.564	0.964	G	A	0.93(0.86, 1.00)	0.062	0.831
rs13428812	*DNMT3A*	G	A	0.95(0.80, 1.13)	0.564	0.964	G	A	1.05(0.96, 1.14)	0.283	0.909
rs3827752	*SLC44A3*	C	A	1.08(0.84, 1.38)	0.566	0.964	C	A	0.97(0.85, 1.10)	0.606	0.969
rs157572	*SLC22A4*	C	G	1.05(0.88, 1.26)	0.567	0.964	G	C	0.95(0.87, 1.04)	0.250	0.902
rs9293761	*DMGDH*	A	G	0.95(0.80, 1.13)	0.568	0.964	A	G	1.01(0.93, 1.09)	0.852	0.979
rs10493879	*SLC44A3*	A	C	0.93(0.72, 1.20)	0.569	0.964	T	G	0.90(0.79, 1.03)	0.127	0.839
rs11667630	*DNMT1*	A	C	1.05(0.89, 1.24)	0.570	0.964	A	C	0.97(0.89, 1.05)	0.419	0.959
rs10925257	*MTR*	G	A	0.94(0.77, 1.15)	0.571	0.964	G	A	1.02(0.93, 1.13)	0.640	0.969
rs2839116	*FTCD*	C	A	1.05(0.88, 1.26)	0.571	0.964	C	A	0.96(0.88, 1.04)	0.323	0.941
rs13070856	*ALDH1L1*	A	G	0.95(0.79, 1.14)	0.571	0.964	--	--	--	--	--
rs1956545	*MTHFD1*	G	A	1.09(0.80, 1.49)	0.573	0.964	T	C	1.16(1.00, 1.35)	0.048	0.823
rs2073066	*MTHFD1L*	C	T	1.07(0.85, 1.33)	0.574	0.964	G	A	1.04(0.94, 1.15)	0.443	0.962
rs1371795	*MTHFD2L*	G	A	0.95(0.80, 1.13)	0.574	0.964	C	T	0.91(0.83, 0.99)	0.037	0.756
rs11724468	*MTHFD2L*	G	A	1.06(0.87, 1.29)	0.574	0.964	A	G	0.94(0.86, 1.03)	0.201	0.892
rs1805087	*MTR*	G	A	0.94(0.77, 1.15)	0.576	0.964	G	A	1.02(0.93, 1.13)	0.683	0.971
rs406193	*DNMT3B*	T	C	0.93(0.73, 1.19)	0.577	0.964	C	T	1.04(0.93, 1.18)	0.478	0.963
rs859057	*SLC44A3*	A	C	0.94(0.76, 1.17)	0.580	0.964	C	A	1.00(0.89, 1.11)	0.949	0.988
rs10465165	*SARDH*	T	G	0.94(0.76, 1.17)	0.580	0.964	--	--	--	--	--
rs11612037	*SHMT2*	T	C	1.11(0.77, 1.60)	0.580	0.964	--	--	--	--	--

RR: Risk Ratio; **CI**: Confidence Interval; **OR**: Odds Ratio; --: Unavailable in replication study

		NENA					CHOP				
SNP	Gene	Minor Allele	Major Allele	RR 95%(CI)	P-value	FDR Q-value	Minor Allele	Major Allele	OR 95%(CI)	P-value	FDR Q-value
rs859104	*SLC44A3*	G	C	1.05(0.89, 1.24)	0.581	0.964	C	G	0.92(0.85, 1.00)	0.044	0.823
rs6923486	*MTHFD1L*	A	G	0.94(0.75, 1.18)	0.582	0.964	G	A	0.94(0.85, 1.04)	0.251	0.902
rs6676866	*MTR*	T	G	1.05(0.89, 1.23)	0.582	0.964	G	T	0.96(0.89, 1.04)	0.364	0.948
rs9325622	*CBS*	G	A	0.95(0.80, 1.13)	0.586	0.964	G	A	1.03(0.95, 1.11)	0.545	0.969
rs817580	*CEPT1*	A	C	1.07(0.85, 1.35)	0.587	0.964	A	C	0.96(0.86, 1.07)	0.417	0.959
rs4659743	*MTR*	A	T	1.05(0.88, 1.24)	0.588	0.964	T	A	1.00(0.92, 1.08)	0.924	0.983
rs3768139	*MTR*	G	C	1.05(0.88, 1.24)	0.588	0.964	C	G	1.00(0.92, 1.08)	0.949	0.988
rs1868128	*ALDH1L1*	A	G	1.05(0.89, 1.24)	0.588	0.964	--	--	--	--	--
rs11102218	*CEPT1*	G	A	1.05(0.89, 1.23)	0.589	0.964	G	A	1.05(0.97, 1.14)	0.223	0.892
rs10802569	*MTR*	G	C	1.05(0.89, 1.24)	0.590	0.964	C	G	0.99(0.91, 1.07)	0.776	0.979
rs10932608	*ATIC*	A	T	1.06(0.86, 1.29)	0.590	0.964	A	T	1.05(0.95, 1.16)	0.304	0.927
rs859081	*SLC44A3*	T	C	0.95(0.77, 1.16)	0.592	0.964	G	A	0.99(0.90, 1.09)	0.807	0.979
rs7518629	*SLC44A5*	T	G	0.96(0.81, 1.13)	0.592	0.964	T	G	1.02(0.94, 1.11)	0.590	0.969
rs12137650	*SLC44A3*	T	C	0.95(0.80, 1.14)	0.593	0.964	T	C	1.03(0.95, 1.12)	0.450	0.962
rs13307588	*NOS3*	A	G	0.90(0.63, 1.30)	0.593	0.964	G	A	1.00(0.85, 1.18)	0.985	0.998
rs471547	*FOLR3*	G	T	1.10(0.79, 1.53)	0.593	0.964	--	--	--	--	--
rs1058151	*TYMS*	G	A	0.96(0.81, 1.13)	0.594	0.964	C	T	0.99(0.91, 1.08)	0.901	0.979
rs7639752	*PCYT1A*	G	A	0.96(0.81, 1.13)	0.596	0.964	A	G	0.95(0.88, 1.03)	0.218	0.892
rs17349743	*MTHFD1L*	C	T	0.95(0.80, 1.14)	0.596	0.964	C	T	0.95(0.88, 1.03)	0.243	0.901
rs10491810	*SLC44A1*	A	T	0.91(0.65, 1.28)	0.597	0.964	T	A	0.96(0.80, 1.14)	0.619	0.969
rs1327873	*CTH*	C	G	0.93(0.70, 1.23)	0.598	0.964	C	G	0.99(0.86, 1.14)	0.901	0.979
rs10887718	*MAT1A*	C	T	0.96(0.82, 1.13)	0.600	0.964	T	C	0.99(0.92, 1.07)	0.872	0.979
rs588885	*CEPT1*	T	A	1.06(0.85, 1.33)	0.602	0.964	T	A	0.99(0.89, 1.10)	0.794	0.979
rs1266164	*MTR*	A	G	1.05(0.88, 1.24)	0.603	0.964	T	C	1.00(0.93, 1.09)	0.908	0.979
rs1013940	*SLC5A7*	C	T	0.93(0.70, 1.23)	0.603	0.964	G	A	1.01(0.87, 1.16)	0.937	0.986
rs7631913	*PCYT1A*	T	C	0.96(0.81, 1.13)	0.603	0.964	C	T	0.97(0.89, 1.04)	0.383	0.948
rs1575219	*MTHFD1L*	A	G	0.95(0.77, 1.17)	0.604	0.964	C	T	0.96(0.87, 1.06)	0.436	0.962
rs12661281	*SLC44A4*	A	T	1.06(0.84, 1.34)	0.604	0.964	--	--	--	--	--
rs13194204	*MTHFD1L*	A	G	1.09(0.79, 1.51)	0.606	0.965	A	G	0.80(0.69, 0.92)	0.002	0.269
rs2114635	*SLC5A7*	G	A	1.04(0.88, 1.23)	0.610	0.967	A	G	0.95(0.87, 1.03)	0.186	0.875
rs4924892	*PEMT*	C	T	1.06(0.85, 1.32)	0.612	0.967	T	C	0.94(0.84, 1.05)	0.279	0.909
rs6795005	*ALDH1L1*	A	G	1.05(0.86, 1.30)	0.613	0.967	--	--	--	--	--
rs681475	*CTH*	A	G	0.96(0.80, 1.14)	0.613	0.967	C	T	0.98(0.90, 1.06)	0.607	0.969
rs7237413	*TYMS*	T	C	1.05(0.87, 1.26)	0.613	0.967	--	--	--	--	--
rs1050993	*MTR*	A	G	1.04(0.88, 1.24)	0.615	0.967	G	A	0.99(0.92, 1.07)	0.821	0.979

RR: Risk Ratio; **CI**: Confidence Interval; **OR**: Odds Ratio; --: Unavailable in replication study

		NENA					CHOP				
SNP	Gene	Minor Allele	Major Allele	RR 95%(CI)	P-value	FDR Q-value	Minor Allele	Major Allele	OR 95%(CI)	P-value	FDR Q-value
rs3099820	*MTHFD2*	T	C	1.06(0.85, 1.32)	0.615	0.967	C	T	1.04(0.94, 1.16)	0.451	0.962
rs1771798	*MTHFD1L*	A	G	1.08(0.81, 1.44)	0.616	0.967	C	T	1.00(0.88, 1.15)	0.983	0.997
rs10179195	*MAT2A*	G	A	1.04(0.88, 1.23)	0.618	0.967	G	A	0.97(0.89, 1.05)	0.404	0.950
rs242542	*DNMT3B*	G	A	0.93(0.71, 1.23)	0.619	0.967	G	A	0.98(0.84, 1.14)	0.802	0.979
rs9842910	*ALDH1L1*	A	G	1.05(0.86, 1.30)	0.619	0.967	--	--	--	--	--
rs129934	*SARDH*	T	C	0.95(0.76, 1.17)	0.625	0.973	--	--	--	--	--
rs2290480	*PLD1*	A	C	1.05(0.86, 1.29)	0.627	0.973	A	C	0.98(0.89, 1.08)	0.662	0.971
rs2662314	*SLC22A4*	T	C	1.06(0.84, 1.34)	0.627	0.973	C	T	0.94(0.84, 1.05)	0.266	0.905
rs731991	*TCN2*	G	A	0.96(0.82, 1.13)	0.629	0.973	G	A	0.94(0.87, 1.02)	0.123	0.837
rs3737967	*MTHFR*	T	C	0.90(0.60, 1.36)	0.629	0.973	A	G	1.04(0.86, 1.25)	0.705	0.977
rs7176987	*MTHFS*	C	A	0.95(0.76, 1.18)	0.633	0.974	C	A	0.97(0.87, 1.08)	0.609	0.969
rs657801	*CEPT1*	C	T	0.96(0.80, 1.14)	0.634	0.974	T	C	1.11(1.02, 1.21)	0.013	0.502
rs2275566	*MTR*	C	T	1.04(0.88, 1.23)	0.637	0.974	A	G	0.99(0.92, 1.08)	0.878	0.979
rs2839111	*FTCD*	T	C	0.95(0.78, 1.16)	0.637	0.974	C	T	1.06(0.96, 1.18)	0.265	0.905
rs803470	*MTHFD1L*	A	G	0.94(0.74, 1.20)	0.637	0.974	C	T	0.94(0.84, 1.05)	0.271	0.905
rs7636149	*PCYT1A*	A	G	1.04(0.88, 1.23)	0.639	0.974	A	G	0.99(0.91, 1.07)	0.762	0.979
rs2275565	*MTR*	A	C	0.95(0.79, 1.16)	0.640	0.974	T	G	1.05(0.96, 1.15)	0.303	0.927
rs13212656	*MTHFD1L*	G	C	0.94(0.74, 1.20)	0.642	0.974	G	C	1.04(0.93, 1.17)	0.488	0.963
rs1889037	*SLC44A5*	G	C	1.04(0.88, 1.23)	0.643	0.974	C	G	0.93(0.86, 1.01)	0.093	0.831
rs2853533	*TYMS*	C	G	1.05(0.84, 1.32)	0.644	0.974	C	G	0.95(0.85, 1.07)	0.412	0.959
rs3768142	*MTR*	G	T	1.04(0.88, 1.23)	0.645	0.974	T	G	0.99(0.92, 1.08)	0.866	0.979
rs4073394	*FOLR3*	G	A	1.04(0.88, 1.23)	0.645	0.974	G	A	0.95(0.88, 1.03)	0.245	0.902
rs7175620	*MTHFS*	C	T	1.04(0.87, 1.26)	0.647	0.974	C	T	1.04(0.95, 1.14)	0.389	0.948
rs11965547	*SLC44A4*	A	G	1.07(0.81, 1.40)	0.648	0.974	A	G	1.09(0.95, 1.25)	0.213	0.892
rs4820886	*TCN2*	G	T	0.94(0.73, 1.22)	0.648	0.974	G	T	0.91(0.80, 1.03)	0.119	0.837
rs11950562	*SLC22A4*	C	A	1.04(0.88, 1.23)	0.649	0.974	C	A	0.86(0.80, 0.94)	0.000	0.074
rs17751556	*MTHFD1*	C	T	0.93(0.68, 1.27)	0.651	0.974	C	T	1.04(0.88, 1.22)	0.675	0.971
rs16853826	*ATIC*	A	G	1.06(0.84, 1.33)	0.651	0.974	A	G	1.10(0.98, 1.23)	0.113	0.837
rs5749131	*TCN2*	A	G	1.04(0.88, 1.23)	0.652	0.974	G	A	0.92(0.85, 1.00)	0.054	0.823
rs17272671	*FTCD*	C	T	1.05(0.84, 1.31)	0.653	0.974	C	T	0.98(0.89, 1.08)	0.711	0.979
rs12483377	*SLC19A1*	A	G	1.07(0.80, 1.41)	0.655	0.974	A	G	0.97(0.84, 1.11)	0.662	0.971
rs4646754	*ALDH1L1*	T	C	0.96(0.81, 1.14)	0.657	0.974	A	G	1.00(0.92, 1.08)	0.965	0.993
rs859088	*SLC44A3*	T	C	0.96(0.80, 1.15)	0.657	0.974	G	A	1.00(0.92, 1.10)	0.942	0.986
rs3747003	*FTCD*	T	C	0.96(0.80, 1.15)	0.658	0.974	T	C	1.00(0.92, 1.09)	0.983	0.997
rs17579604	*SLC44A3*	G	A	0.95(0.77, 1.18)	0.658	0.974	G	A	1.00(0.90, 1.11)	0.929	0.983

RR: Risk Ratio; **CI**: Confidence Interval; **OR**: Odds Ratio; --: Unavailable in replication study

		NENA					CHOP				
SNP	Gene	Minor Allele	Major Allele	RR 95%(CI)	P-value	FDR Q-value	Minor Allele	Major Allele	OR 95%(CI)	P-value	FDR Q-value
rs13002567	*DNMT3A*	C	T	1.04(0.86, 1.26)	0.659	0.974	C	T	1.00(0.92, 1.09)	0.928	0.983
rs437302	*DNMT3B*	A	G	0.94(0.71, 1.25)	0.660	0.974	A	G	0.97(0.85, 1.10)	0.601	0.969
rs10181373	*SLC5A7*	A	C	0.96(0.80, 1.15)	0.663	0.978	C	A	1.01(0.92, 1.10)	0.842	0.979
rs2307116	*MTRR*	T	C	0.96(0.80, 1.15)	0.667	0.981	A	G	1.05(0.97, 1.14)	0.225	0.892
rs6940322	*MTHFD1L*	T	A	0.96(0.81, 1.14)	0.668	0.981	T	A	1.07(0.98, 1.16)	0.123	0.837
rs2236222	*MTHFD1*	C	T	0.94(0.70, 1.26)	0.669	0.981	G	A	0.81(0.71, 0.94)	0.004	0.339
rs466791	*CBS*	T	C	0.95(0.75, 1.21)	0.673	0.984	T	C	1.03(0.92, 1.15)	0.619	0.969
rs1571983	*SLC44A5*	C	T	0.96(0.81, 1.15)	0.676	0.984	G	A	1.01(0.92, 1.10)	0.891	0.979
rs474244	*SLC22A2*	T	C	1.04(0.86, 1.26)	0.677	0.984	G	A	0.98(0.90, 1.07)	0.653	0.971
rs1885031	*MTHFD1*	G	A	0.94(0.71, 1.25)	0.679	0.984	T	C	1.08(0.94, 1.25)	0.272	0.905
rs402894	*CBS*	C	T	1.04(0.86, 1.25)	0.679	0.984	C	T	0.99(0.91, 1.08)	0.831	0.979
rs616827	*SLC44A5*	G	T	1.04(0.87, 1.25)	0.679	0.984	T	G	0.99(0.90, 1.08)	0.760	0.979
rs3754255	*MTR*	T	C	1.03(0.88, 1.22)	0.680	0.984	T	C	0.98(0.90, 1.06)	0.570	0.969
rs11911976	*CBS*	C	T	0.96(0.81, 1.15)	0.680	0.984	T	C	0.98(0.91, 1.06)	0.680	0.971
rs181715	*PLD1*	A	T	0.97(0.81, 1.14)	0.683	0.984	T	A	0.99(0.92, 1.08)	0.867	0.979
rs3849303	*SLC44A3*	T	C	0.95(0.75, 1.21)	0.683	0.984	A	G	0.90(0.80, 1.01)	0.085	0.831
rs1770449	*MTR*	G	A	1.04(0.87, 1.23)	0.684	0.984	C	T	1.00(0.93, 1.09)	0.959	0.993
rs12211869	*MTHFD1L*	T	G	0.96(0.81, 1.15)	0.688	0.984	T	G	0.96(0.88, 1.05)	0.371	0.948
rs6058896	*DNMT3B*	T	C	1.08(0.75, 1.54)	0.688	0.984	T	C	0.99(0.84, 1.17)	0.920	0.983
rs688120	*CEPT1*	A	T	0.97(0.81, 1.15)	0.690	0.984	A	T	1.11(1.02, 1.21)	0.012	0.502
rs1263781	*CHPT1*	T	A	0.97(0.82, 1.14)	0.692	0.984	--	--	--	--	--
rs1072389	*MTHFD2L*	A	G	0.96(0.81, 1.15)	0.692	0.984	--	--	--	--	--
rs234706	*CBS*	A	G	1.04(0.87, 1.24)	0.692	0.984	A	G	1.03(0.95, 1.12)	0.444	0.962
rs6923669	*MTHFD1L*	G	A	1.05(0.83, 1.32)	0.695	0.984	G	A	1.03(0.92, 1.15)	0.638	0.969
rs3764899	*PLD2*	T	C	0.97(0.81, 1.15)	0.697	0.984	A	G	1.05(0.97, 1.14)	0.229	0.892
rs13183229	*MTRR*	A	G	0.97(0.82, 1.15)	0.700	0.984	A	G	0.96(0.88, 1.04)	0.295	0.915
rs16961114	*SHMT1*	C	G	0.96(0.80, 1.17)	0.701	0.984	C	G	0.98(0.90, 1.07)	0.671	0.971
rs162024	*MTRR*	G	T	0.97(0.82, 1.14)	0.703	0.984	T	G	0.93(0.86, 1.00)	0.053	0.823
rs2844458	*SLC44A4*	T	G	1.03(0.87, 1.22)	0.704	0.984	A	C	0.98(0.89, 1.06)	0.571	0.969
rs10991622	*SLC44A1*	C	T	0.92(0.59, 1.42)	0.705	0.984	C	T	0.98(0.77, 1.26)	0.897	0.979
rs11235468	*FOLR2*	G	T	1.05(0.82, 1.34)	0.705	0.984	G	T	0.94(0.83, 1.06)	0.323	0.941
rs1249837	*SLC44A5*	A	G	1.03(0.87, 1.22)	0.705	0.984	T	C	1.04(0.96, 1.13)	0.339	0.943
rs11155760	*MTHFD1L*	T	A	1.03(0.87, 1.23)	0.706	0.984	T	A	0.94(0.86, 1.03)	0.185	0.875
rs10158990	*SLC44A5*	G	C	0.97(0.82, 1.14)	0.707	0.984	C	G	0.94(0.87, 1.02)	0.122	0.837
rs328006	*SLC44A1*	C	G	1.05(0.80, 1.39)	0.709	0.984	C	G	1.11(0.96, 1.28)	0.162	0.854

RR: Risk Ratio; **CI**: Confidence Interval; **OR**: Odds Ratio; --: Unavailable in replication study

		NENA					CHOP				
SNP	Gene	Minor Allele	Major Allele	RR 95%(CI)	P-value	FDR Q-value	Minor Allele	Major Allele	OR 95%(CI)	P-value	FDR Q-value
rs2330183	*SLC19A1*	C	T	0.97(0.82, 1.15)	0.710	0.984	T	C	1.01(0.93, 1.09)	0.887	0.979
rs9332	*MTRR*	T	C	1.05(0.82, 1.33)	0.710	0.984	A	G	0.87(0.78, 0.99)	0.028	0.689
rs5753220	*TCN2*	C	T	0.97(0.80, 1.16)	0.713	0.984	C	T	1.08(0.99, 1.18)	0.083	0.831
rs2490334	*CEPT1*	A	G	0.97(0.81, 1.15)	0.715	0.984	G	A	1.10(1.01, 1.19)	0.030	0.689
rs9840089	*PCYT1A*	G	A	0.97(0.82, 1.15)	0.716	0.984	A	G	0.96(0.88, 1.03)	0.239	0.901
rs859074	*SLC44A3*	T	C	1.03(0.87, 1.23)	0.716	0.984	--	--	--	--	--
rs2427988	*SARDH*	T	C	0.95(0.74, 1.23)	0.717	0.984	--	--	--	--	--
rs17226802	*BHMT2*	C	A	1.09(0.68, 1.75)	0.717	0.984	C	A	1.01(0.78, 1.30)	0.960	0.993
rs83615	*PLD1*	G	A	0.96(0.77, 1.20)	0.718	0.984	A	G	0.98(0.88, 1.10)	0.747	0.979
rs4451422	*FPGS*	C	A	1.03(0.87, 1.22)	0.719	0.984	C	A	1.02(0.94, 1.11)	0.610	0.969
rs316171	*SLC22A3*	T	G	0.97(0.82, 1.15)	0.721	0.984	A	C	1.03(0.95, 1.12)	0.458	0.963
rs4934027	*MAT1A*	T	C	0.97(0.79, 1.17)	0.722	0.984	T	C	0.96(0.87, 1.06)	0.404	0.950
rs2427995	*SARDH*	T	G	0.95(0.71, 1.27)	0.723	0.984	--	--	--	--	--
rs83616	*PLD1*	G	A	1.03(0.87, 1.22)	0.724	0.984	A	G	0.97(0.90, 1.05)	0.488	0.963
rs3820571	*MTR*	G	T	1.03(0.87, 1.22)	0.724	0.984	T	G	0.99(0.92, 1.08)	0.865	0.979
rs7686861	*MTHFD2L*	C	T	1.03(0.87, 1.22)	0.725	0.984	--	--	--	--	--
rs6799991	*ALDH1L1*	A	G	1.03(0.87, 1.21)	0.727	0.984	--	--	--	--	--
rs4573897	*MTHFS*	A	G	1.03(0.87, 1.22)	0.727	0.984	A	G	1.05(0.97, 1.14)	0.214	0.892
rs2619268	*SLC22A2*	A	C	0.97(0.80, 1.17)	0.728	0.984	G	T	0.94(0.86, 1.03)	0.185	0.875
rs9901160	*SHMT1*	A	G	0.96(0.77, 1.20)	0.728	0.984	A	G	1.00(0.90, 1.12)	0.937	0.986
rs2839127	*FTCD*	A	G	1.04(0.83, 1.30)	0.728	0.984	G	A	0.96(0.86, 1.06)	0.398	0.949
rs803447	*MTHFD1L*	T	C	0.97(0.82, 1.14)	0.729	0.984	G	A	1.01(0.93, 1.09)	0.840	0.979
rs2586167	*MTHFS*	T	C	0.97(0.81, 1.16)	0.729	0.984	A	G	0.96(0.88, 1.04)	0.273	0.905
rs7552892	*SLC44A3*	T	C	0.96(0.77, 1.21)	0.736	0.988	T	C	1.20(1.08, 1.34)	0.001	0.170
rs2298444	*FOLR2*	G	A	0.97(0.79, 1.18)	0.737	0.988	C	T	1.04(0.94, 1.15)	0.448	0.962
rs2850146	*CBS*	G	C	0.95(0.70, 1.28)	0.739	0.988	G	C	0.91(0.79, 1.05)	0.191	0.885
rs2073836	*SARDH*	A	T	1.03(0.87, 1.23)	0.739	0.988	--	--	--	--	--
rs3790715	*CEPT1*	C	T	0.96(0.74, 1.24)	0.743	0.988	G	A	0.95(0.84, 1.07)	0.421	0.959
rs162899	*SLC22A4*	G	A	0.97(0.81, 1.16)	0.743	0.988	G	A	1.09(1.00, 1.20)	0.061	0.831
rs11892646	*DNMT3A*	T	C	1.04(0.82, 1.33)	0.745	0.988	T	C	0.94(0.83, 1.06)	0.302	0.927
rs10515456	*SLC22A5*	A	G	1.05(0.79, 1.38)	0.747	0.988	A	G	1.10(0.97, 1.25)	0.150	0.839
rs6464119	*NOS3*	T	C	0.97(0.79, 1.19)	0.748	0.988	C	T	1.07(0.97, 1.19)	0.161	0.854
rs333216	*SLC5A7*	T	C	0.97(0.81, 1.16)	0.751	0.988	A	G	0.97(0.89, 1.06)	0.528	0.969
rs614549	*SLC44A4*	C	T	1.03(0.87, 1.21)	0.752	0.988	G	A	0.98(0.90, 1.07)	0.627	0.969
rs7715062	*MTRR*	T	G	0.97(0.82, 1.15)	0.752	0.988	T	G	0.94(0.87, 1.02)	0.166	0.854

RR: Risk Ratio; **CI**: Confidence Interval; **OR**: Odds Ratio; --: Unavailable in replication study

		NENA					CHOP				
SNP	Gene	Minor Allele	Major Allele	RR 95%(CI)	P-value	FDR Q-value	Minor Allele	Major Allele	OR 95%(CI)	P-value	FDR Q-value
rs7280485	*FTCD*	A	G	1.03(0.86, 1.23)	0.753	0.988	A	G	1.01(0.93, 1.10)	0.763	0.979
rs11656215	*PEMT*	T	C	1.03(0.87, 1.21)	0.753	0.988	T	C	0.98(0.91, 1.07)	0.672	0.971
rs3772423	*ALDH1L1*	A	C	0.97(0.79, 1.18)	0.754	0.988	T	G	1.04(0.94, 1.14)	0.472	0.963
rs9371494	*MTHFD1L*	G	A	1.03(0.86, 1.23)	0.754	0.988	A	G	0.96(0.88, 1.04)	0.326	0.942
rs2283125	*SARDH*	A	C	1.03(0.86, 1.22)	0.754	0.988	--	--	--	--	--
rs6668344	*MTR*	T	C	1.03(0.87, 1.21)	0.755	0.988	T	C	0.95(0.88, 1.03)	0.225	0.892
rs10026687	*MTHFD2L*	C	T	1.03(0.84, 1.26)	0.758	0.988	C	T	1.05(0.96, 1.15)	0.313	0.928
rs10887721	*MAT1A*	C	G	1.04(0.82, 1.31)	0.758	0.988	C	G	1.06(0.95, 1.19)	0.285	0.909
rs2303629	*CHPT1*	G	C	0.97(0.82, 1.16)	0.759	0.988	--	--	--	--	--
rs17004785	*SLC19A1*	C	G	1.04(0.81, 1.34)	0.761	0.988	C	G	0.98(0.86, 1.12)	0.749	0.979
rs1738575	*MTHFD1L*	G	C	0.98(0.83, 1.14)	0.762	0.988	G	C	0.94(0.87, 1.02)	0.142	0.839
rs2073833	*SARDH*	G	C	1.03(0.87, 1.21)	0.767	0.988	--	--	--	--	--
rs10874305	*SLC44A5*	T	C	1.03(0.84, 1.26)	0.768	0.988	T	C	0.94(0.86, 1.04)	0.236	0.901
rs12175302	*MTHFD1L*	C	G	1.04(0.79, 1.38)	0.768	0.988	C	G	1.03(0.90, 1.18)	0.688	0.972
rs6087982	*DNMT3B*	G	A	1.03(0.85, 1.25)	0.769	0.988	G	A	0.98(0.89, 1.08)	0.627	0.969
rs17780078	*CHPT1*	A	G	1.06(0.72, 1.55)	0.774	0.988	--	--	--	--	--
rs4855877	*AMT*	G	A	0.98(0.83, 1.15)	0.775	0.988	C	T	1.01(0.93, 1.09)	0.818	0.979
rs190024	*SLC44A5*	C	A	1.03(0.84, 1.26)	0.775	0.988	A	C	0.95(0.86, 1.05)	0.309	0.927
rs13089568	*ALDH1L1*	A	G	1.02(0.87, 1.20)	0.775	0.988	--	--	--	--	--
rs2510257	*SARDH*	A	C	1.03(0.85, 1.25)	0.776	0.988	--	--	--	--	--
rs706209	*CBS*	T	C	0.98(0.82, 1.15)	0.777	0.988	A	G	1.04(0.96, 1.13)	0.358	0.948
rs11924478	*ALDH1L1*	T	C	1.03(0.85, 1.24)	0.777	0.988	--	--	--	--	--
rs16988828	*TCN2*	G	A	0.96(0.74, 1.25)	0.778	0.988	G	A	1.01(0.89, 1.15)	0.887	0.979
rs3826785	*DNMT1*	T	C	1.04(0.81, 1.33)	0.778	0.988	T	C	1.02(0.89, 1.16)	0.778	0.979
rs502396	*TYMS*	C	T	1.02(0.87, 1.20)	0.779	0.988	T	C	1.07(0.99, 1.15)	0.069	0.831
rs7281816	*FTCD*	T	C	0.97(0.76, 1.23)	0.779	0.988	T	C	1.07(0.95, 1.19)	0.266	0.905
rs2586181	*MTHFS*	T	C	1.04(0.80, 1.35)	0.780	0.988	G	A	1.03(0.91, 1.17)	0.670	0.971
rs10196635	*DNMT3A*	T	A	1.04(0.79, 1.37)	0.780	0.988	T	A	1.01(0.88, 1.15)	0.893	0.979
rs6009931	*CHKB*	G	T	0.95(0.69, 1.32)	0.780	0.988	G	T	0.96(0.82, 1.11)	0.551	0.969
rs4659723	*MTR*	T	C	0.97(0.76, 1.23)	0.780	0.988	T	C	1.01(0.90, 1.13)	0.850	0.979
rs4869984	*MTHFD1L*	T	C	1.02(0.87, 1.21)	0.781	0.988	T	C	1.01(0.94, 1.10)	0.764	0.979
rs3819255	*CHKA*	A	T	0.98(0.82, 1.16)	0.784	0.988	T	A	0.93(0.86, 1.01)	0.092	0.831
rs12565150	*SLC44A3*	A	T	0.97(0.79, 1.19)	0.785	0.988	A	T	0.92(0.83, 1.02)	0.103	0.831
rs2839121	*FTCD*	G	C	0.97(0.79, 1.20)	0.786	0.988	G	C	1.02(0.92, 1.13)	0.733	0.979
rs12661373	*MTHFD1L*	A	G	1.03(0.85, 1.24)	0.788	0.988	A	G	0.98(0.90, 1.07)	0.643	0.971

RR: Risk Ratio; **CI**: Confidence Interval; **OR**: Odds Ratio; --: Unavailable in replication study

		NENA					CHOP				
SNP	Gene	Minor Allele	Major Allele	RR 95%(CI)	P-value	FDR Q-value	Minor Allele	Major Allele	OR 95%(CI)	P-value	FDR Q-value
rs2424898	*DNMT3B*	C	T	1.03(0.85, 1.24)	0.788	0.988	C	T	0.98(0.89, 1.07)	0.610	0.969
rs828863	*MTHFD2*	A	G	1.04(0.77, 1.41)	0.788	0.988	T	C	0.96(0.84, 1.10)	0.573	0.969
rs2230491	*MTHFD1*	T	C	1.03(0.81, 1.32)	0.789	0.988	T	C	1.01(0.90, 1.14)	0.839	0.979
rs11751336	*MTHFD1L*	C	G	0.95(0.66, 1.37)	0.793	0.992	C	G	1.02(0.86, 1.19)	0.856	0.979
rs634841	*MTHFS*	T	C	1.03(0.82, 1.29)	0.795	0.993	T	C	0.96(0.86, 1.06)	0.401	0.949
rs11587108	*SLC44A3*	T	C	1.03(0.83, 1.27)	0.797	0.994	T	C	0.91(0.82, 1.02)	0.095	0.831
rs16837183	*ALDH1L1*	C	T	0.95(0.64, 1.41)	0.799	0.995	--	--	--	--	--
rs7560488	*DNMT3A*	C	T	1.02(0.87, 1.20)	0.800	0.995	C	T	1.08(1.00, 1.17)	0.053	0.823
rs1076504	*PLD1*	G	C	1.03(0.84, 1.25)	0.801	0.995	G	C	0.98(0.89, 1.08)	0.640	0.969
rs8128028	*CBS*	T	C	0.98(0.82, 1.17)	0.803	0.995	T	C	0.98(0.90, 1.07)	0.640	0.969
rs7769613	*MTHFD1L*	A	G	0.97(0.80, 1.19)	0.805	0.995	A	G	1.00(0.91, 1.10)	0.997	0.998
rs7349940	*MTHFD1L*	A	T	0.97(0.75, 1.25)	0.807	0.995	A	T	0.94(0.82, 1.07)	0.331	0.943
rs12202291	*MTHFD1L*	G	A	0.98(0.82, 1.17)	0.809	0.995	G	A	1.02(0.94, 1.12)	0.615	0.969
rs10066017	*MTRR*	G	T	1.02(0.85, 1.23)	0.812	0.995	G	T	1.05(0.97, 1.15)	0.251	0.902
rs11165263	*SLC44A3*	C	T	0.98(0.80, 1.20)	0.813	0.995	C	T	0.94(0.85, 1.04)	0.228	0.892
rs7700970	*BHMT*	T	C	1.02(0.85, 1.23)	0.817	0.995	T	C	0.97(0.88, 1.06)	0.470	0.963
rs4979632	*SARDH*	T	C	1.02(0.84, 1.24)	0.818	0.995	--	--	--	--	--
rs12205664	*MTHFD1L*	T	C	1.05(0.71, 1.55)	0.819	0.995	T	C	0.83(0.68, 1.03)	0.087	0.831
rs6271	*SARDH*	T	C	1.04(0.75, 1.43)	0.820	0.995	--	--	--	--	--
rs6446976	*MTHFD2L*	C	G	0.96(0.68, 1.36)	0.820	0.995	G	C	0.98(0.80, 1.20)	0.868	0.979
rs2057519	*SLC44A5*	G	A	0.98(0.83, 1.16)	0.822	0.995	G	A	1.06(0.97, 1.15)	0.194	0.891
rs7594432	*DNMT3A*	C	T	0.98(0.83, 1.16)	0.823	0.995	C	T	0.98(0.91, 1.07)	0.704	0.977
rs17567259	*SLC44A5*	G	A	1.04(0.72, 1.52)	0.824	0.995	G	A	1.08(0.91, 1.29)	0.370	0.948
rs881883	*CHDH*	C	T	1.03(0.81, 1.29)	0.824	0.995	G	A	1.15(1.02, 1.30)	0.018	0.548
rs10483080	*SLC19A1*	G	C	1.03(0.81, 1.31)	0.825	0.995	G	C	0.96(0.85, 1.08)	0.468	0.963
rs9974320	*FTCD*	A	G	1.02(0.85, 1.23)	0.826	0.995	A	G	1.03(0.93, 1.14)	0.581	0.969
rs175864	*MTHFD1L*	A	C	0.97(0.71, 1.31)	0.829	0.995	T	G	1.16(0.97, 1.38)	0.101	0.831
rs9978174	*FTCD*	C	G	0.98(0.83, 1.17)	0.831	0.995	C	G	0.99(0.90, 1.09)	0.840	0.979
rs2733088	*MTHFS*	A	G	0.98(0.83, 1.16)	0.833	0.995	A	G	0.96(0.88, 1.04)	0.271	0.905
rs6586282	*CBS*	T	C	1.02(0.82, 1.29)	0.833	0.995	T	C	0.99(0.89, 1.09)	0.823	0.979
rs7238	*CHKB*	C	T	0.97(0.74, 1.27)	0.833	0.995	--	--	--	--	--
rs9606756	*TCN2*	G	A	0.97(0.76, 1.24)	0.834	0.995	G	A	0.96(0.85, 1.09)	0.535	0.969
rs2342309	*PCYT1A*	T	C	0.98(0.82, 1.18)	0.835	0.995	T	C	0.95(0.87, 1.04)	0.252	0.902
rs316029	*SLC22A2*	T	C	0.97(0.76, 1.25)	0.835	0.995	C	T	0.96(0.86, 1.08)	0.529	0.969
rs559088	*DMGDH*	C	G	1.02(0.86, 1.21)	0.836	0.995	C	G	1.01(0.93, 1.10)	0.765	0.979

RR: Risk Ratio; **CI**: Confidence Interval; **OR**: Odds Ratio; --: Unavailable in replication study

		NENA					CHOP				
SNP	Gene	Minor Allele	Major Allele	RR 95%(CI)	P-value	FDR Q-value	Minor Allele	Major Allele	OR 95%(CI)	P-value	FDR Q-value
rs575341	*FOLR3*	A	G	0.97(0.76, 1.25)	0.839	0.995	C	T	1.05(0.92, 1.20)	0.471	0.963
rs6775861	*PCYT1A*	T	C	1.03(0.74, 1.45)	0.842	0.995	T	C	1.04(0.88, 1.22)	0.643	0.971
rs6557111	*MTHFD1L*	A	G	1.02(0.85, 1.22)	0.845	0.995	G	A	0.95(0.88, 1.04)	0.258	0.905
rs77905	*SARDH*	T	C	1.02(0.86, 1.20)	0.846	0.995	--	--	--	--	--
rs11203172	*CBS*	T	G	1.02(0.82, 1.28)	0.847	0.995	T	G	1.04(0.93, 1.16)	0.476	0.963
rs13194929	*MTHFD1L*	G	A	1.02(0.84, 1.24)	0.849	0.995	G	A	0.98(0.89, 1.07)	0.637	0.969
rs35020344	*MTHFD1*	G	A	1.02(0.86, 1.20)	0.850	0.995	G	A	0.98(0.91, 1.06)	0.685	0.972
rs11953102	*DMGDH*	C	G	0.98(0.80, 1.20)	0.855	0.995	C	G	0.96(0.87, 1.06)	0.443	0.962
rs2286670	*PLD2*	A	C	1.02(0.81, 1.29)	0.859	0.995	T	G	0.98(0.88, 1.10)	0.747	0.979
rs13069815	*ALDH1L1*	A	C	0.98(0.74, 1.29)	0.862	0.995	--	--	--	--	--
rs2073063	*MTHFD1L*	C	T	1.02(0.86, 1.20)	0.863	0.995	G	A	0.99(0.92, 1.08)	0.865	0.979
rs1128162	*SLC46A1*	G	T	1.01(0.86, 1.20)	0.864	0.995	A	C	0.95(0.88, 1.03)	0.219	0.892
rs182411	*SLC44A5*	A	G	0.98(0.81, 1.19)	0.864	0.995	G	A	0.98(0.90, 1.08)	0.742	0.979
rs2164411	*DNMT3A*	T	C	0.98(0.79, 1.21)	0.864	0.995	A	G	0.97(0.87, 1.07)	0.522	0.967
rs828858	*MTHFD2*	A	T	1.01(0.86, 1.20)	0.865	0.995	A	T	1.02(0.94, 1.10)	0.674	0.971
rs853858	*DNMT3B*	A	G	1.01(0.86, 1.19)	0.866	0.995	A	G	1.01(0.93, 1.09)	0.838	0.979
rs1541332	*SARDH*	T	C	0.99(0.84, 1.16)	0.866	0.995	--	--	--	--	--
rs4869970	*MTHFD1L*	G	A	1.03(0.75, 1.40)	0.867	0.995	G	A	0.90(0.76, 1.08)	0.263	0.905
rs2242665	*SLC44A4*	G	A	0.99(0.84, 1.16)	0.867	0.995	T	C	1.01(0.93, 1.10)	0.817	0.979
rs859072	*SLC44A3*	G	A	0.98(0.80, 1.21)	0.870	0.995	T	C	1.00(0.90, 1.11)	0.965	0.993
rs2993763	*MAT1A*	A	G	0.99(0.83, 1.17)	0.871	0.995	A	G	0.96(0.89, 1.04)	0.346	0.943
rs6424386	*CTH*	A	T	0.98(0.76, 1.26)	0.871	0.995	A	T	0.93(0.82, 1.05)	0.240	0.901
rs1045075	*PCYT1A*	T	C	0.99(0.84, 1.16)	0.872	0.995	A	G	0.94(0.87, 1.02)	0.116	0.837
rs2073815	*SARDH*	C	T	1.01(0.86, 1.19)	0.872	0.995	--	--	--	--	--
rs4659724	*MTR*	A	G	0.99(0.83, 1.17)	0.873	0.995	A	G	0.94(0.87, 1.02)	0.167	0.854
rs933683	*DMGDH*	T	G	0.99(0.82, 1.18)	0.874	0.995	T	G	0.95(0.88, 1.04)	0.287	0.909
rs161869	*MTRR*	T	C	1.01(0.86, 1.20)	0.876	0.995	T	C	1.02(0.94, 1.10)	0.686	0.972
rs7873937	*SLC44A1*	C	G	1.02(0.77, 1.35)	0.877	0.995	C	G	1.04(0.92, 1.18)	0.515	0.965
rs211688	*SLC44A5*	A	C	0.98(0.81, 1.20)	0.877	0.995	C	A	0.97(0.88, 1.07)	0.532	0.969
rs4820874	*TCN2*	G	A	0.98(0.79, 1.23)	0.878	0.995	G	A	1.05(0.94, 1.17)	0.388	0.948
rs2070578	*FTCD*	T	C	0.99(0.84, 1.17)	0.878	0.995	T	C	1.04(0.96, 1.13)	0.298	0.923
rs4077829	*MTR*	T	G	0.99(0.84, 1.17)	0.879	0.995	T	G	0.95(0.88, 1.03)	0.222	0.892
rs234709	*CBS*	T	C	1.01(0.85, 1.20)	0.880	0.995	T	C	1.01(0.94, 1.10)	0.728	0.979
rs360402	*PLD1*	G	A	0.99(0.82, 1.19)	0.883	0.995	A	G	0.98(0.90, 1.06)	0.562	0.969
rs4920037	*CBS*	A	G	1.01(0.83, 1.25)	0.892	0.995	A	G	0.99(0.91, 1.09)	0.867	0.979

RR: Risk Ratio; **CI**: Confidence Interval; **OR**: Odds Ratio; --: Unavailable in replication study

		NENA					CHOP				
SNP	Gene	Minor Allele	Major Allele	RR 95%(CI)	P-value	FDR Q-value	Minor Allele	Major Allele	OR 95%(CI)	P-value	FDR Q-value
rs7555627	*SLC44A5*	G	A	0.99(0.83, 1.18)	0.893	0.995	G	A	0.92(0.84, 1.00)	0.053	0.823
rs273909	*SLC22A4*	C	T	1.02(0.78, 1.33)	0.893	0.995	G	A	1.09(0.95, 1.24)	0.215	0.892
rs12614943	*ATIC*	G	A	0.99(0.82, 1.19)	0.894	0.995	G	A	1.04(0.95, 1.13)	0.446	0.962
rs2350631	*PEMT*	T	C	0.99(0.84, 1.17)	0.894	0.995	C	T	1.03(0.96, 1.12)	0.418	0.959
rs4646745	*ALDH1L1*	T	C	0.99(0.81, 1.21)	0.896	0.995	A	G	1.10(1.00, 1.21)	0.048	0.823
rs12941217	*PEMT*	A	G	1.01(0.85, 1.20)	0.897	0.995	A	G	1.03(0.95, 1.12)	0.419	0.959
rs1052751	*PLD2*	A	G	1.01(0.81, 1.27)	0.897	0.995	A	G	1.08(0.97, 1.19)	0.162	0.854
rs8118663	*DNMT3B*	G	A	0.99(0.82, 1.20)	0.899	0.995	G	A	1.00(0.91, 1.10)	0.965	0.993
rs11676382	*MAT2A*	G	C	1.02(0.76, 1.36)	0.900	0.995	G	C	1.13(0.98, 1.30)	0.098	0.831
rs2027963	*SARDH*	A	C	0.99(0.84, 1.17)	0.901	0.995	--	--	--	--	--
rs381870	*SLC22A4*	T	A	1.01(0.83, 1.24)	0.902	0.995	T	A	1.15(1.04, 1.27)	0.007	0.441
rs3788205	*SLC19A1*	T	C	1.01(0.84, 1.22)	0.903	0.995	C	T	1.04(0.95, 1.13)	0.392	0.948
rs12626746	*FTCD*	T	C	0.99(0.84, 1.17)	0.904	0.995	C	T	1.02(0.94, 1.11)	0.674	0.971
rs756682	*SARDH*	G	A	0.99(0.84, 1.17)	0.904	0.995	--	--	--	--	--
rs4819210	*FTCD*	A	G	0.99(0.82, 1.20)	0.904	0.995	G	A	1.06(0.96, 1.17)	0.224	0.892
rs3815743	*MTRR*	G	A	1.01(0.82, 1.26)	0.904	0.995	G	A	0.98(0.88, 1.08)	0.651	0.971
rs6780561	*PLD1*	G	A	0.99(0.84, 1.17)	0.905	0.995	A	G	0.99(0.91, 1.07)	0.776	0.979
rs12038630	*SLC44A3*	A	G	1.01(0.81, 1.28)	0.905	0.995	A	G	0.95(0.85, 1.07)	0.412	0.959
rs478651	*DMGDH*	G	A	0.99(0.84, 1.17)	0.906	0.995	C	T	0.98(0.90, 1.06)	0.560	0.969
rs3805673	*SLC22A4*	A	G	0.98(0.74, 1.31)	0.906	0.995	A	G	1.20(1.03, 1.39)	0.018	0.548
rs10874314	*SLC44A5*	A	G	1.01(0.86, 1.19)	0.907	0.995	G	A	0.93(0.86, 1.00)	0.064	0.831
rs685487	*MTHFS*	C	T	1.01(0.85, 1.20)	0.907	0.995	G	A	0.96(0.89, 1.04)	0.336	0.943
rs3204635	*SHMT2*	T	C	0.99(0.82, 1.19)	0.908	0.995	A	G	1.03(0.94, 1.13)	0.481	0.963
rs17112592	*SLC44A3*	G	A	1.01(0.83, 1.24)	0.909	0.995	G	A	0.95(0.84, 1.06)	0.355	0.948
rs9478847	*MTHFD1L*	C	T	1.02(0.70, 1.49)	0.909	0.995	C	T	1.10(0.91, 1.34)	0.325	0.942
rs1611123	*SARDH*	A	G	0.99(0.84, 1.17)	0.912	0.995	--	--	--	--	--
rs12209109	*MTHFD1L*	C	T	0.99(0.83, 1.18)	0.912	0.995	C	T	1.00(0.92, 1.09)	0.988	0.998
rs1789953	*CBS*	T	C	1.01(0.81, 1.26)	0.917	0.995	T	C	1.02(0.92, 1.14)	0.662	0.971
rs7525338	*MTHFR*	T	C	0.94(0.28, 3.18)	0.917	0.995	--	--	--	--	--
rs17719944	*SLC46A1*	G	A	1.02(0.75, 1.38)	0.918	0.995	G	A	0.98(0.85, 1.13)	0.797	0.979
rs579283	*MTHFD1L*	T	C	0.99(0.84, 1.17)	0.919	0.995	A	G	1.07(0.99, 1.16)	0.096	0.831
rs509474	*MTHFD1L*	C	G	0.99(0.84, 1.17)	0.920	0.995	G	C	1.02(0.95, 1.11)	0.569	0.969
rs9322298	*MTHFD1L*	G	C	1.02(0.72, 1.43)	0.920	0.995	G	C	0.89(0.75, 1.07)	0.211	0.892
rs328012	*SLC44A1*	G	T	0.99(0.82, 1.20)	0.921	0.995	C	A	1.13(1.02, 1.24)	0.016	0.533
rs486416	*SLC44A4*	C	T	0.99(0.82, 1.19)	0.921	0.995	--	--	--	--	--

RR: Risk Ratio; **CI**: Confidence Interval; **OR**: Odds Ratio; --: Unavailable in replication study

		NENA					CHOP				
SNP	Gene	Minor Allele	Major Allele	RR 95%(CI)	P-value	FDR Q-value	Minor Allele	Major Allele	OR 95%(CI)	P-value	FDR Q-value
rs506500	*BHMT*	T	C	1.01(0.84, 1.21)	0.921	0.995	C	T	0.99(0.91, 1.07)	0.742	0.979
rs740234	*TCN2*	C	T	1.01(0.82, 1.24)	0.922	0.995	G	A	0.92(0.83, 1.01)	0.083	0.831
rs1077872	*NOS3*	C	G	0.99(0.84, 1.17)	0.923	0.995	C	G	1.01(0.92, 1.10)	0.902	0.979
rs7523188	*CTH*	G	A	0.99(0.81, 1.21)	0.924	0.995	G	A	0.95(0.86, 1.05)	0.288	0.909
rs672413	*DMGDH*	T	C	1.01(0.85, 1.20)	0.925	0.995	G	A	1.07(0.98, 1.16)	0.130	0.839
rs7029443	*SLC44A1*	A	T	1.01(0.80, 1.27)	0.925	0.995	A	T	1.04(0.92, 1.17)	0.575	0.969
rs524732	*MTHFD1L*	T	C	1.01(0.83, 1.22)	0.925	0.995	A	G	1.06(0.96, 1.16)	0.260	0.905
rs12773664	*MAT1A*	G	A	0.99(0.84, 1.17)	0.925	0.995	G	A	1.08(1.00, 1.17)	0.056	0.831
rs162048	*MTRR*	G	A	0.99(0.78, 1.25)	0.928	0.995	A	G	0.92(0.83, 1.02)	0.112	0.837
rs156110	*SLC22A4*	G	C	0.99(0.77, 1.28)	0.930	0.995	C	G	1.11(0.97, 1.26)	0.121	0.837
rs943199	*SLC44A3*	G	T	0.99(0.83, 1.19)	0.930	0.995	T	G	1.03(0.95, 1.13)	0.487	0.963
rs7757336	*SLC22A2*	G	T	1.01(0.80, 1.28)	0.932	0.995	G	T	1.01(0.91, 1.13)	0.834	0.979
rs2289209	*CHDH*	A	G	0.99(0.70, 1.38)	0.932	0.995	T	C	1.27(1.04, 1.55)	0.017	0.548
rs955516	*MTR*	A	T	0.99(0.84, 1.17)	0.932	0.995	A	T	0.95(0.87, 1.02)	0.166	0.854
rs3849306	*SLC44A3*	A	C	0.99(0.79, 1.24)	0.933	0.995	T	G	0.90(0.81, 1.01)	0.075	0.831
rs12129440	*MTR*	A	G	0.99(0.82, 1.20)	0.933	0.995	A	G	1.02(0.94, 1.12)	0.625	0.969
rs6445607	*CHDH*	G	T	0.99(0.84, 1.18)	0.936	0.995	T	G	1.00(0.92, 1.08)	0.908	0.979
rs1131603	*TCN2*	C	T	1.02(0.68, 1.52)	0.936	0.995	C	T	1.06(0.87, 1.28)	0.562	0.969
rs10889869	*CTH*	A	G	1.01(0.74, 1.39)	0.938	0.995	A	G	0.99(0.86, 1.14)	0.929	0.983
rs1593685	*SLC5A7*	G	C	0.99(0.74, 1.32)	0.939	0.995	C	G	1.07(0.92, 1.24)	0.370	0.948
rs13050660	*FTCD*	T	C	0.99(0.83, 1.19)	0.939	0.995	C	T	1.03(0.95, 1.11)	0.539	0.969
rs2241933	*PLD2*	T	G	1.01(0.84, 1.20)	0.941	0.995	G	T	0.99(0.91, 1.07)	0.771	0.979
rs17407097	*SLC44A3*	G	A	1.01(0.80, 1.27)	0.941	0.995	G	A	0.95(0.85, 1.06)	0.388	0.948
rs17292141	*FTCD*	G	A	1.01(0.75, 1.37)	0.942	0.995	G	A	0.99(0.86, 1.13)	0.850	0.979
rs494620	*SLC44A4*	A	G	1.01(0.85, 1.19)	0.944	0.995	A	G	0.97(0.89, 1.05)	0.482	0.963
rs9874508	*ALDH1L1*	A	G	0.99(0.84, 1.17)	0.946	0.995	--	--	--	--	--
rs11612551	*SHMT2*	A	G	1.01(0.84, 1.21)	0.946	0.995	--	--	--	--	--
rs12060570	*MTR*	C	G	0.99(0.84, 1.18)	0.951	0.995	C	G	0.95(0.88, 1.03)	0.221	0.892
rs17112682	*SLC44A3*	G	A	1.01(0.72, 1.42)	0.953	0.995	G	A	1.02(0.82, 1.27)	0.870	0.979
rs326123	*MTRR*	G	A	1.00(0.84, 1.18)	0.953	0.995	A	G	0.99(0.92, 1.08)	0.859	0.979
rs316024	*SLC22A2*	A	G	1.01(0.84, 1.20)	0.954	0.995	T	C	0.96(0.88, 1.04)	0.344	0.943
rs12053233	*MTHFD2*	T	C	1.01(0.84, 1.21)	0.956	0.995	T	C	1.01(0.93, 1.10)	0.743	0.979
rs5997711	*TCN2*	T	C	1.00(0.84, 1.18)	0.957	0.995	C	T	0.94(0.87, 1.02)	0.132	0.839
rs529087	*MTHFD1L*	T	C	1.01(0.83, 1.22)	0.958	0.995	A	G	1.02(0.93, 1.12)	0.673	0.971
rs12185084	*MTHFS*	A	G	0.99(0.81, 1.22)	0.959	0.995	A	G	0.99(0.90, 1.09)	0.803	0.979

RR: Risk Ratio; **CI**: Confidence Interval; **OR**: Odds Ratio; --: Unavailable in replication study

		NENA					CHOP				
SNP	Gene	Minor Allele	Major Allele	RR 95%(CI)	P-value	FDR Q-value	Minor Allele	Major Allele	OR 95%(CI)	P-value	FDR Q-value
rs10925252	*MTR*	C	T	1.00(0.84, 1.18)	0.959	0.995	C	T	0.96(0.88, 1.04)	0.270	0.905
rs9804151	*CTH*	C	T	0.99(0.80, 1.23)	0.959	0.995	C	T	1.02(0.93, 1.13)	0.631	0.969
rs12032960	*SLC44A3*	C	T	1.01(0.82, 1.23)	0.960	0.995	C	T	0.95(0.87, 1.05)	0.352	0.943
rs4328397	*MTHFS*	C	T	1.01(0.79, 1.28)	0.960	0.995	C	T	1.07(0.95, 1.20)	0.287	0.909
rs10493878	*SLC44A3*	G	A	0.99(0.80, 1.24)	0.961	0.995	C	T	0.94(0.85, 1.05)	0.262	0.905
rs10778137	*CHPT1*	A	G	1.00(0.83, 1.19)	0.961	0.995	--	--	--	--	--
rs2075798	*SLC44A4*	T	G	1.01(0.73, 1.39)	0.962	0.995	A	C	1.07(0.91, 1.25)	0.437	0.962
rs9383552	*MTHFD1L*	G	A	1.01(0.72, 1.41)	0.962	0.995	G	A	0.90(0.75, 1.07)	0.222	0.892
rs234784	*CBS*	T	C	1.00(0.85, 1.19)	0.964	0.995	C	T	0.98(0.90, 1.06)	0.605	0.969
rs2612092	*TYMS*	A	G	0.99(0.76, 1.30)	0.964	0.995	T	C	0.94(0.86, 1.02)	0.122	0.837
rs4646750	*ALDH1L1*	G	A	0.99(0.73, 1.34)	0.964	0.995	C	T	1.11(0.95, 1.28)	0.185	0.875
rs10501409	*FOLR1*	C	A	1.01(0.77, 1.31)	0.964	0.995	G	T	0.96(0.84, 1.10)	0.585	0.969
rs12528219	*MTHFD1L*	C	G	0.99(0.78, 1.28)	0.966	0.995	C	G	1.02(0.90, 1.17)	0.730	0.979
rs1806505	*MTR*	T	C	1.00(0.84, 1.18)	0.969	0.995	T	C	0.95(0.88, 1.03)	0.226	0.892
rs3935460	*CHKA*	G	A	1.00(0.84, 1.18)	0.971	0.995	T	C	1.09(1.01, 1.18)	0.033	0.720
rs803446	*MTHFD1L*	T	C	1.00(0.82, 1.21)	0.972	0.995	A	G	1.03(0.94, 1.14)	0.513	0.965
rs162023	*MTRR*	A	G	1.00(0.85, 1.17)	0.973	0.995	--	--	--	--	--
rs762684	*MAT2A*	T	C	1.00(0.83, 1.19)	0.974	0.995	A	G	0.97(0.89, 1.06)	0.464	0.963
rs2293160	*PCYT1A*	C	T	1.00(0.84, 1.19)	0.974	0.995	C	T	1.01(0.93, 1.09)	0.885	0.979
rs2297702	*CEPT1*	T	C	0.99(0.71, 1.39)	0.974	0.995	A	G	0.98(0.83, 1.16)	0.808	0.979
rs380691	*DHFR*	C	T	1.00(0.84, 1.19)	0.976	0.995	G	A	0.99(0.91, 1.07)	0.802	0.979
rs17689550	*SLC22A5*	T	C	1.00(0.77, 1.30)	0.976	0.995	T	C	1.04(0.91, 1.18)	0.586	0.969
rs9982015	*CBS*	C	T	1.00(0.72, 1.37)	0.976	0.995	C	T	0.94(0.82, 1.08)	0.395	0.948
rs2665355	*SLC22A3*	C	G	1.00(0.85, 1.18)	0.977	0.995	C	G	0.99(0.92, 1.07)	0.814	0.979
rs1667627	*MTHFD2*	G	A	1.00(0.85, 1.18)	0.979	0.995	T	C	0.99(0.92, 1.07)	0.844	0.979
rs9966612	*TYMS*	A	G	1.00(0.83, 1.19)	0.980	0.995	G	A	0.93(0.85, 1.01)	0.080	0.831
rs585800	*BHMT*	T	A	1.00(0.82, 1.21)	0.981	0.995	A	T	1.00(0.91, 1.09)	0.918	0.983
rs9478157	*MTHFD1L*	G	T	1.00(0.85, 1.19)	0.981	0.995	G	T	1.05(0.96, 1.14)	0.285	0.909
rs3772431	*ALDH1L1*	A	G	1.00(0.84, 1.18)	0.983	0.996	C	T	0.98(0.90, 1.07)	0.660	0.971
rs12134663	*MTHFR*	C	A	1.00(0.79, 1.26)	0.984	0.996	C	A	1.05(0.95, 1.16)	0.368	0.948
rs333226	*SLC5A7*	G	A	1.00(0.79, 1.27)	0.987	0.997	A	G	0.99(0.88, 1.10)	0.841	0.979
rs2502745	*SARDH*	C	G	1.00(0.85, 1.18)	0.991	0.997	--	--	--	--	--
rs3733075	*CHDH*	T	C	1.00(0.85, 1.18)	0.991	0.997	T	C	0.97(0.89, 1.05)	0.460	0.963
rs1801133	*MTHFR*	T	C	1.00(0.84, 1.19)	0.992	0.997	A	G	0.92(0.85, 1.00)	0.059	0.831

RR: Risk Ratio; **CI**: Confidence Interval; **OR**: Odds Ratio; --: Unavailable in replication study

		NENA					CHOP				
SNP	Gene	Minor Allele	Major Allele	RR 95%(CI)	P-value	FDR Q-value	Minor Allele	Major Allele	OR 95%(CI)	P-value	FDR Q-value
rs698962	*SLC44A3*	A	G	1.00(0.82, 1.23)	0.994	0.997	T	C	0.91(0.83, 1.00)	0.059	0.831
rs11082	*CHPT1*	G	A	1.00(0.85, 1.18)	0.995	0.997	--	--	--	--	--
rs9432593	*SLC44A3*	G	A	1.00(0.83, 1.21)	0.995	0.997	G	A	0.94(0.86, 1.03)	0.188	0.883
rs2851391	*CBS*	T	C	1.00(0.85, 1.18)	0.996	0.997	C	T	1.03(0.95, 1.12)	0.427	0.962
rs13212150	*MTHFD1L*	C	T	1.00(0.84, 1.19)	0.996	0.997	C	T	0.98(0.90, 1.07)	0.637	0.969
rs16948305	*TYMS*	T	C	1.00(0.79, 1.27)	0.998	0.998	T	C	0.96(0.87, 1.06)	0.453	0.962

RR: Risk Ratio **CI**: Confidence Interval; **OR**: Odd Ratio; --: Unavailable in replication study

APPENDIX 4. RESULTS FROM MATERNAL FOLATE AND CHOLINE-RELATED SNPS

SNP	Gene	Minor Allele	Major Allele	RR (95% CI)	P-value	Q-value
rs2302327	*PLD2*	A	G	1.70(1.23,2.34)	0.001	0.502
rs3123634	*SLC22A3*	T	C	1.34(1.14,1.58)	0.001	0.459
rs316174	*SLC22A3*	T	C	1.30(1.10,1.54)	0.002	0.502
rs803456	*MTHFD1L*	C	T	0.78(0.66,0.92)	0.003	0.621
rs663649	*CTH*	T	G	1.30(1.08,1.57)	0.006	0.785
rs17421462	*MTHFR*	A	G	0.65(0.48,0.89)	0.007	0.785
rs4869087	*MAT2B*	C	A	1.29(1.07,1.55)	0.007	0.785
rs604745	*SLC44A5*	G	T	0.76(0.62,0.94)	0.010	0.785
rs3797546	*BHMT*	C	T	1.65(1.12,2.44)	0.012	0.785
rs2221750	*SLC22A3*	A	G	1.29(1.05,1.58)	0.014	0.785
rs2424922	*DNMT3B*	C	T	1.23(1.04,1.46)	0.016	0.785
rs11202403	*MAT1A*	T	C	1.29(1.05,1.59)	0.017	0.785
rs17806489	*SHMT1*	A	G	0.73(0.56,0.94)	0.017	0.785
rs2083868	*SLC44A5*	G	A	0.79(0.65,0.96)	0.018	0.785
rs4819208	*FTCD*	G	A	1.28(1.04,1.57)	0.018	0.785
rs7642538	*ALDH1L1*	A	G	0.79(0.65,0.96)	0.018	0.785
rs17080476	*MTHFD1L*	G	A	0.77(0.62,0.96)	0.019	0.785
rs712208	*MTHFD1L*	T	C	0.78(0.63,0.96)	0.019	0.785
rs7733775	*MAT2B*	A	G	1.22(1.03,1.45)	0.019	0.785
rs4708867	*SLC22A3*	G	A	1.38(1.05,1.80)	0.021	0.785
rs1979277	*SHMT1*	A	G	1.23(1.03,1.47)	0.022	0.785
rs2504937	*SLC22A3*	G	C	0.81(0.68,0.97)	0.023	0.785
rs2504956	*SLC22A3*	A	G	0.78(0.63,0.97)	0.023	0.785
rs13373826	*SLC44A5*	G	A	0.76(0.60,0.97)	0.024	0.785
rs1650697	*DHFR*	T	C	0.80(0.65,0.98)	0.027	0.785
rs1967613	*ATIC*	A	T	1.22(1.02,1.46)	0.029	0.785
rs7604984	*ATIC*	G	A	1.20(1.02,1.42)	0.029	0.785
rs17375901	*MTHFR*	T	C	1.51(1.03,2.20)	0.033	0.785
rs4646703	*ALDH1L1*	A	G	0.77(0.61,0.98)	0.033	0.785
rs3798156	*SLC22A2*	A	G	1.32(1.02,1.70)	0.034	0.785
rs512077	*SLC22A3*	A	G	1.27(1.02,1.59)	0.034	0.785
rs519861	*MTHFD1L*	C	T	1.26(1.02,1.56)	0.035	0.785
rs1004053	*SLC44A5*	G	A	0.83(0.70,0.99)	0.036	0.785
rs3120137	*SLC22A3*	T	C	1.31(1.02,1.68)	0.036	0.785
rs7722729	*MAT2B*	C	T	1.27(1.01,1.58)	0.038	0.785
rs627494	*SLC44A5*	G	T	0.84(0.71,0.99)	0.039	0.785
rs661620	*DMGDH*	C	T	0.84(0.71,0.99)	0.041	0.785
rs2283124	*SARDH*	T	C	1.31(1.01,1.71)	0.042	0.785
rs11663153	*TYMS*	A	C	1.22(1.01,1.48)	0.043	0.785
rs17591295	*SLC22A3*	A	G	1.47(1.01,2.14)	0.045	0.785
rs1771845	*MTHFD1L*	T	C	0.84(0.71,1.00)	0.046	0.785
rs2048327	*SLC22A3*	G	A	1.20(1.00,1.42)	0.046	0.785
rs28365862	*SHMT2*	G	A	1.48(1.01,2.18)	0.046	0.785
rs11040265	*FOLH1*	T	C	1.34(1.00,1.79)	0.047	0.785
rs12995526	*ATIC*	T	C	0.85(0.72,1.00)	0.048	0.785
rs3127575	*SLC22A2*	T	C	1.30(1.00,1.70)	0.048	0.785
rs3918227	*NOS3*	A	C	1.37(1.00,1.86)	0.048	0.785
rs129886	*SARDH*	T	C	0.82(0.68,1.00)	0.049	0.785
rs8016556	*MTHFD1*	C	T	0.84(0.71,1.00)	0.049	0.785

RR: Risk ratio; **CI**: Confidence interval

SNP	Gene	Minor Allele	Major Allele	RR (95% CI)	P-value	Q-value
rs8127036	*CBS*	T	C	0.80(0.63,1.00)	0.050	0.785
rs11755049	*MTHFD1L*	T	A	0.76(0.58,1.00)	0.052	0.785
rs4709432	*SLC22A3*	G	A	1.24(1.00,1.55)	0.053	0.785
rs891512	*NOS3*	A	G	0.82(0.66,1.00)	0.054	0.785
rs2273027	*SHMT1*	A	G	0.85(0.71,1.00)	0.055	0.785
rs7081756	*MAT1A*	G	T	1.18(1.00,1.40)	0.055	0.785
rs10821578	*SARDH*	T	C	1.17(1.00,1.37)	0.056	0.785
rs11908812	*FTCD*	A	G	1.33(0.99,1.78)	0.056	0.785
rs1205349	*AHCY*	C	G	1.28(0.99,1.63)	0.056	0.785
rs316169	*SLC22A3*	A	C	1.19(1.00,1.42)	0.056	0.785
rs11080058	*SLC46A1*	A	G	0.84(0.69,1.01)	0.057	0.785
rs13063848	*PLD1*	A	G	1.31(0.99,1.73)	0.057	0.785
rs140514	*CHKB*	C	T	1.17(1.00,1.38)	0.057	0.785
rs7556057	*SLC44A5*	T	C	0.83(0.69,1.01)	0.057	0.785
rs1544920	*CHPT1*	T	C	0.79(0.61,1.01)	0.058	0.785
rs3755817	*CHDH*	C	T	1.19(0.99,1.43)	0.059	0.785
rs2457552	*SLC22A3*	T	G	0.82(0.67,1.01)	0.060	0.785
rs13317328	*CHDH*	C	A	0.77(0.58,1.01)	0.061	0.785
rs612893	*DMGDH*	A	G	0.85(0.72,1.01)	0.061	0.785
rs2303080	*MTRR*	A	T	1.55(0.98,2.47)	0.062	0.785
rs3733890	*BHMT*	A	G	0.84(0.70,1.01)	0.065	0.812
rs2909854	*BHMT*	C	G	0.85(0.71,1.01)	0.067	0.829
rs1567441	*SLC22A3*	G	A	0.83(0.68,1.01)	0.069	0.833
rs7533315	*MTHFR*	T	C	0.84(0.69,1.02)	0.071	0.833
rs1891902	*SLC44A5*	T	C	0.85(0.71,1.01)	0.072	0.833
rs2295638	*MTHFD1*	T	C	0.66(0.42,1.04)	0.072	0.833
rs569919	*SLC22A3*	T	C	0.84(0.70,1.02)	0.076	0.833
rs1950902	*MTHFD1*	T	C	0.82(0.66,1.02)	0.078	0.833
rs3788190	*SLC19A1*	A	G	0.86(0.73,1.02)	0.079	0.833
rs6753886	*SLC5A7*	A	G	0.86(0.72,1.02)	0.081	0.833
rs10515861	*MAT2B*	C	T	0.85(0.71,1.02)	0.083	0.833
rs1112444	*SLC22A3*	A	C	1.18(0.98,1.42)	0.083	0.833
rs17588242	*SLC22A2*	C	T	0.84(0.69,1.02)	0.083	0.833
rs803455	*MTHFD1L*	T	C	0.73(0.51,1.04)	0.083	0.833
rs11595587	*MAT1A*	A	G	0.63(0.38,1.06)	0.084	0.833
rs11664283	*TYMS*	A	G	1.18(0.98,1.43)	0.086	0.833
rs17080461	*MTHFD1L*	T	C	0.80(0.61,1.03)	0.088	0.833
rs492842	*BHMT*	G	A	0.87(0.73,1.02)	0.090	0.833
rs2137407	*SLC44A5*	A	G	1.41(0.95,2.11)	0.091	0.833
rs4847361	*SLC44A3*	C	T	0.81(0.63,1.04)	0.091	0.833
rs3794186	*CHKA*	T	C	1.33(0.95,1.86)	0.092	0.833
rs7289549	*TCN2*	C	G	1.23(0.97,1.57)	0.092	0.833
rs2304429	*DNMT3A*	G	A	0.87(0.73,1.03)	0.093	0.833
rs316176	*SLC22A3*	G	A	0.86(0.72,1.03)	0.094	0.833
rs1580820	*PCYT1A*	C	T	0.81(0.63,1.04)	0.095	0.833
rs299299	*MAT2B*	G	T	1.20(0.97,1.50)	0.095	0.833
rs4846048	*MTHFR*	G	A	0.86(0.72,1.03)	0.095	0.833
rs6668699	*MTHFR*	C	T	0.86(0.73,1.03)	0.095	0.833
rs6814380	*MTHFD2L*	G	C	1.16(0.98,1.37)	0.095	0.833
rs8019804	*MTHFD1*	G	T	1.32(0.95,1.84)	0.095	0.833
rs7730643	*MTRR*	G	A	1.21(0.97,1.52)	0.096	0.833
rs2287779	*MTRR*	A	G	1.43(0.93,2.18)	0.100	0.833
rs248381	*DMGDH*	A	G	1.15(0.97,1.35)	0.100	0.833

RR: Risk ratio; **CI**: Confidence interval

SNP	Gene	Minor Allele	Major Allele	RR (95% CI)	P-value	Q-value
rs1249655	*SLC44A5*	A	T	1.16(0.97,1.39)	0.101	0.833
rs140516	*CHKB*	A	G	1.18(0.97,1.45)	0.101	0.833
rs17689595	*SLC22A5*	A	G	0.83(0.67,1.04)	0.102	0.833
rs819144	*AHCY*	T	G	1.24(0.96,1.60)	0.102	0.833
rs9687295	*DMGDH*	G	A	0.83(0.66,1.04)	0.102	0.833
rs2007053	*GART*	C	T	1.18(0.97,1.44)	0.104	0.833
rs2424932	*DNMT3B*	A	G	0.87(0.73,1.03)	0.105	0.833
rs9669539	*CHPT1*	C	T	1.17(0.97,1.40)	0.105	0.833
rs505358	*MTHFD1L*	T	C	1.16(0.97,1.39)	0.106	0.833
rs7545324	*SLC44A5*	G	A	1.18(0.97,1.45)	0.107	0.835
rs17269293	*SLC5A7*	G	C	1.20(0.96,1.49)	0.109	0.843
rs333241	*SLC5A7*	T	C	0.85(0.69,1.04)	0.112	0.861
rs10791958	*CHKA*	T	A	1.24(0.95,1.63)	0.114	0.864
rs939885	*PCYT1A*	G	A	0.88(0.75,1.03)	0.114	0.864
rs9968875	*MTHFD1L*	G	A	0.81(0.63,1.05)	0.117	0.876
rs2298582	*TYMS*	C	A	0.82(0.64,1.05)	0.118	0.876
rs8130986	*CBS*	A	G	1.23(0.95,1.58)	0.120	0.886
rs11163496	*SLC44A5*	T	C	0.85(0.68,1.05)	0.126	0.92
rs10265237	*NOS3*	A	G	1.16(0.96,1.39)	0.127	0.922
rs1363730	*MAT2B*	T	C	1.20(0.94,1.54)	0.141	0.945
rs162889	*SLC22A4*	T	C	0.87(0.72,1.05)	0.141	0.945
rs12217395	*MAT1A*	A	G	1.15(0.96,1.38)	0.142	0.945
rs17354394	*MTHFD1L*	G	A	1.28(0.92,1.78)	0.142	0.945
rs1537514	*MTHFR*	G	C	1.23(0.93,1.62)	0.143	0.945
rs2236225	*MTHFD1*	T	C	1.13(0.96,1.33)	0.143	0.945
rs17448447	*ATIC*	G	A	1.14(0.96,1.35)	0.144	0.945
rs705415	*DMGDH*	A	G	1.21(0.94,1.57)	0.144	0.945
rs16879334	*MTRR*	G	C	1.37(0.90,2.11)	0.146	0.945
rs4869713	*MTHFD1L*	C	T	0.89(0.75,1.04)	0.146	0.945
rs4934028	*MAT1A*	A	G	0.88(0.75,1.05)	0.147	0.945
rs4659718	*MTR*	C	A	0.88(0.74,1.05)	0.148	0.945
rs9397365	*MTHFD1L*	T	C	0.84(0.67,1.06)	0.148	0.945
rs1073083	*CHPT1*	T	A	0.87(0.71,1.05)	0.149	0.945
rs12626309	*GART*	T	A	0.86(0.71,1.05)	0.149	0.945
rs16876394	*DMGDH*	C	T	1.23(0.93,1.63)	0.149	0.945
rs9478918	*MTHFD1L*	T	C	0.83(0.65,1.07)	0.150	0.945
rs472703	*MTHFD1L*	G	A	0.85(0.68,1.06)	0.151	0.945
rs698966	*SLC44A3*	G	T	0.88(0.75,1.05)	0.152	0.945
rs1232027	*DHFR*	A	G	1.14(0.95,1.35)	0.153	0.945
rs12637288	*PCYT1A*	G	A	0.89(0.75,1.05)	0.154	0.945
rs250513	*DMGDH*	T	C	0.87(0.72,1.06)	0.156	0.945
rs12275064	*FOLH1*	T	G	1.19(0.94,1.51)	0.158	0.945
rs884534	*PCYT1A*	T	C	0.87(0.71,1.06)	0.159	0.945
rs2041149	*CHPT1*	G	A	1.13(0.95,1.34)	0.160	0.945
rs2797836	*SARDH*	A	G	1.12(0.96,1.32)	0.161	0.945
rs514933	*FOLR2*	G	A	1.13(0.95,1.33)	0.163	0.945
rs735937	*SLC44A3*	G	A	1.13(0.95,1.33)	0.163	0.945
rs12037733	*SLC44A3*	A	G	0.87(0.71,1.06)	0.164	0.945
rs42418	*DMGDH*	G	C	1.12(0.95,1.33)	0.164	0.945
rs476235	*SLC22A2*	T	C	0.88(0.74,1.05)	0.164	0.945
rs576075	*SLC22A2*	T	C	0.88(0.73,1.06)	0.165	0.945
rs175853	*MTHFD1L*	T	C	1.13(0.95,1.35)	0.167	0.951
rs12733999	*CTH*	T	C	1.36(0.88,2.10)	0.169	0.951

RR: Risk ratio; **CI**: Confidence interval

SNP	Gene	Minor Allele	Major Allele	RR (95% CI)	P-value	Q-value
rs9306264	*TCN2*	T	C	1.23(0.91,1.67)	0.169	0.951
rs2295640	*MTHFD1*	G	C	0.82(0.62,1.09)	0.173	0.957
rs742829	*MTHFD1L*	G	A	1.16(0.94,1.44)	0.173	0.957
rs12469531	*SLC5A7*	C	T	0.80(0.57,1.11)	0.178	0.964
rs17520351	*SLC44A3*	T	C	0.79(0.57,1.11)	0.178	0.964
rs4270463	*ALDH1L1*	T	C	1.31(0.88,1.95)	0.179	0.964
rs1036145	*NOS3*	A	G	0.89(0.75,1.06)	0.181	0.964
rs642013	*DMGDH*	T	C	0.89(0.74,1.06)	0.185	0.964
rs1570191	*MTHFD1L*	C	T	1.22(0.91,1.64)	0.186	0.964
rs2741186	*TYMS*	T	C	0.90(0.76,1.06)	0.192	0.964
rs7770982	*MTHFD1L*	G	A	0.84(0.64,1.09)	0.193	0.964
rs2695284	*CHPT1*	C	T	0.90(0.76,1.06)	0.199	0.964
rs4911263	*DNMT3B*	T	C	0.89(0.75,1.06)	0.200	0.964
rs6893970	*BHMT*	A	G	1.20(0.91,1.57)	0.200	0.964
rs906713	*CHKA*	A	G	0.87(0.70,1.08)	0.200	0.964
rs1915706	*BHMT*	T	C	1.12(0.94,1.33)	0.201	0.964
rs11185518	*PCYT1A*	T	C	0.86(0.68,1.08)	0.203	0.964
rs2853741	*TYMS*	T	C	1.12(0.94,1.33)	0.204	0.964
rs698964	*SLC44A3*	A	G	1.12(0.94,1.33)	0.207	0.964
rs129902	*SARDH*	C	G	1.16(0.92,1.45)	0.211	0.964
rs6058897	*DNMT3B*	A	C	0.90(0.77,1.06)	0.213	0.964
rs12745827	*CEPT1*	G	T	1.16(0.92,1.47)	0.214	0.964
rs175860	*MTHFD1L*	A	C	0.90(0.76,1.06)	0.214	0.964
rs4911107	*DNMT3B*	A	G	1.11(0.94,1.32)	0.214	0.964
rs495139	*TYMS*	G	C	0.90(0.76,1.06)	0.216	0.964
rs1050152	*SLC22A4*	T	C	1.11(0.94,1.32)	0.217	0.964
rs315984	*SLC22A2*	C	T	1.13(0.93,1.37)	0.217	0.964
rs3016432	*FOLR1*	G	A	1.11(0.94,1.31)	0.218	0.964
rs2450282	*SLC5A7*	A	G	0.79(0.54,1.15)	0.220	0.964
rs8142477	*CHKB*	C	G	0.87(0.69,1.09)	0.221	0.964
rs1021737	*CTH*	T	G	0.89(0.74,1.07)	0.222	0.964
rs41385949	*SLC44A5*	A	G	0.79(0.53,1.16)	0.222	0.964
rs10078190	*DHFR*	T	C	1.19(0.90,1.59)	0.224	0.964
rs10179904	*MAT2A*	A	G	1.17(0.91,1.51)	0.225	0.964
rs4694666	*MTHFD2L*	C	T	1.21(0.89,1.63)	0.225	0.964
rs1023159	*SLC19A1*	A	G	0.90(0.76,1.07)	0.226	0.964
rs11746555	*SLC22A5*	A	G	1.11(0.94,1.32)	0.226	0.964
rs803454	*MTHFD1L*	A	G	0.83(0.61,1.13)	0.229	0.964
rs10489810	*SLC44A3*	T	A	0.90(0.75,1.07)	0.230	0.964
rs652888	*SLC44A4*	C	T	0.88(0.71,1.09)	0.231	0.964
rs4120874	*MTR*	G	A	0.88(0.70,1.09)	0.232	0.964
rs1980983	*FTCD*	G	A	0.90(0.75,1.07)	0.235	0.964
rs4894499	*PLD1*	C	T	0.88(0.72,1.08)	0.235	0.964
rs12438477	*MTHFS*	A	C	0.91(0.77,1.07)	0.239	0.964
rs11951068	*DMGDH*	A	G	1.19(0.89,1.58)	0.240	0.964
rs1047665	*MTHFD1L*	G	A	1.23(0.87,1.72)	0.242	0.964
rs12912711	*MTHFS*	A	G	1.19(0.89,1.58)	0.242	0.964
rs2243393	*CEPT1*	T	C	0.90(0.76,1.07)	0.242	0.964
rs596881	*SLC22A2*	A	G	0.86(0.66,1.11)	0.242	0.964
rs12401888	*SLC44A5*	T	C	1.16(0.90,1.51)	0.245	0.964
rs2299644	*FOLH1*	T	C	0.85(0.65,1.12)	0.245	0.964
rs6693082	*CTH*	G	T	0.90(0.74,1.08)	0.245	0.964
rs10489586	*SLC44A5*	A	G	0.78(0.51,1.19)	0.247	0.964

RR: Risk ratio; **CI**: Confidence interval

SNP	Gene	Minor Allele	Major Allele	RR (95% CI)	P-value	Q-value
rs4563403	*CHDH*	T	C	0.87(0.68,1.10)	0.247	0.964
rs2236484	*SLC19A1*	A	G	0.91(0.77,1.07)	0.248	0.964
rs2880456	*MAT1A*	T	G	0.85(0.64,1.12)	0.248	0.964
rs3795823	*CEPT1*	T	C	1.12(0.93,1.35)	0.251	0.964
rs4817575	*GART*	A	G	0.86(0.66,1.11)	0.251	0.964
rs1249839	*SLC44A5*	T	C	1.11(0.93,1.32)	0.253	0.964
rs7586969	*ATIC*	G	A	0.91(0.77,1.07)	0.256	0.964
rs11654690	*PLD2*	A	G	0.84(0.62,1.14)	0.257	0.964
rs2484459	*CEPT1*	C	G	0.89(0.72,1.09)	0.257	0.964
rs2797853	*SARDH*	A	G	0.90(0.76,1.08)	0.257	0.964
rs13214952	*MTHFD1L*	G	T	0.90(0.75,1.08)	0.258	0.964
rs2431332	*DMGDH*	G	A	0.89(0.73,1.09)	0.258	0.964
rs4818789	*SLC19A1*	G	T	0.90(0.74,1.08)	0.258	0.964
rs9290428	*PLD1*	G	C	0.91(0.77,1.07)	0.260	0.964
rs4646755	*ALDH1L1*	C	A	0.90(0.74,1.09)	0.261	0.964
rs3886314	*SLC44A3*	A	C	1.10(0.93,1.31)	0.262	0.964
rs631305	*BHMT*	A	G	0.88(0.70,1.10)	0.263	0.964
rs6721036	*SLC5A7*	T	C	0.86(0.66,1.12)	0.263	0.964
rs4245407	*FOLR3*	A	G	1.10(0.93,1.29)	0.264	0.964
rs8076949	*SLC46A1*	T	C	1.18(0.88,1.57)	0.265	0.964
rs6479643	*SARDH*	C	G	0.91(0.77,1.08)	0.266	0.964
rs333231	*SLC5A7*	A	G	1.11(0.92,1.34)	0.268	0.964
rs4687747	*CHDH*	T	G	1.18(0.88,1.59)	0.268	0.964
rs12201472	*MTHFD1L*	T	C	1.17(0.89,1.55)	0.269	0.964
rs12636371	*ALDH1L1*	A	G	0.91(0.77,1.08)	0.269	0.964
rs12210887	*SLC44A4*	T	G	0.82(0.58,1.16)	0.270	0.964
rs1557502	*CHKB*	A	G	0.90(0.73,1.09)	0.272	0.964
rs6766988	*CHDH*	A	T	0.86(0.66,1.13)	0.272	0.964
rs7237052	*TYMS*	A	C	1.10(0.93,1.30)	0.272	0.964
rs7550014	*SLC44A3*	T	C	0.89(0.71,1.10)	0.272	0.964
rs36027301	*CHKA*	T	C	0.81(0.55,1.18)	0.273	0.964
rs2373929	*NOS3*	T	C	1.10(0.93,1.29)	0.275	0.964
rs13060596	*ALDH1L1*	T	G	0.91(0.77,1.08)	0.277	0.964
rs2288350	*DNMT1*	T	C	0.85(0.63,1.14)	0.280	0.964
rs7596024	*DNMT3A*	A	G	1.10(0.93,1.30)	0.280	0.964
rs140515	*CHKB*	C	G	0.91(0.77,1.08)	0.281	0.964
rs3119309	*SLC22A2*	T	C	1.16(0.89,1.51)	0.281	0.964
rs13401241	*DNMT3A*	C	A	1.09(0.93,1.29)	0.282	0.964
rs6546045	*DNMT3A*	C	T	1.10(0.92,1.32)	0.282	0.964
rs2295084	*MTHFD1L*	A	G	1.14(0.90,1.43)	0.285	0.964
rs4256166	*PLD1*	T	C	0.90(0.75,1.09)	0.285	0.964
rs3120976	*MAT1A*	C	A	0.91(0.76,1.08)	0.287	0.964
rs316033	*SLC22A2*	G	A	1.10(0.92,1.31)	0.288	0.964
rs6141803	*DNMT3B*	C	T	1.13(0.91,1.40)	0.288	0.964
rs836788	*DHFR*	A	G	0.91(0.77,1.08)	0.288	0.964
rs129883	*SARDH*	G	C	1.10(0.92,1.32)	0.289	0.964
rs7717	*FTCD*	C	G	1.13(0.90,1.43)	0.289	0.964
rs9870993	*ALDH1L1*	T	G	1.10(0.92,1.30)	0.290	0.964
rs10204232	*ATIC*	A	C	1.18(0.87,1.61)	0.295	0.964
rs9267658	*SLC44A4*	T	C	1.14(0.89,1.48)	0.297	0.964
rs10380	*MTRR*	T	C	1.15(0.89,1.48)	0.299	0.964
rs1889036	*SLC44A5*	G	T	1.11(0.92,1.33)	0.299	0.964
rs4147779	*CHKA*	G	A	0.90(0.75,1.09)	0.300	0.964

RR: Risk ratio; **CI**: Confidence interval

SNP	Gene	Minor Allele	Major Allele	RR (95% CI)	P-value	Q-value
rs4847362	*SLC44A3*	A	G	0.91(0.76,1.09)	0.301	0.964
rs6495449	*MTHFS*	A	G	0.87(0.66,1.14)	0.301	0.964
rs6760069	*ATIC*	A	G	0.88(0.70,1.12)	0.302	0.964
rs893363	*CHDH*	C	T	1.09(0.92,1.30)	0.302	0.964
rs11754661	*MTHFD1L*	A	G	0.84(0.59,1.18)	0.304	0.964
rs35592604	*SLC44A5*	T	C	1.12(0.90,1.40)	0.309	0.964
rs1044988	*PCYT1A*	C	T	1.11(0.91,1.36)	0.311	0.964
rs333214	*SLC5A7*	C	T	1.13(0.89,1.43)	0.311	0.964
rs668641	*MTHFS*	A	G	1.09(0.92,1.28)	0.311	0.964
rs1405312	*SLC44A5*	T	C	1.13(0.89,1.42)	0.312	0.964
rs336520	*DMGDH*	A	G	1.13(0.89,1.44)	0.315	0.964
rs2586183	*MTHFS*	T	A	0.92(0.78,1.08)	0.316	0.964
rs3806531	*SLC5A7*	G	A	1.09(0.92,1.29)	0.316	0.964
rs8065874	*SHMT1*	T	C	0.91(0.75,1.10)	0.318	0.964
rs4120852	*MAT1A*	C	A	0.92(0.77,1.09)	0.319	0.964
rs2834233	*GART*	G	A	1.15(0.87,1.52)	0.320	0.964
rs4646748	*ALDH1L1*	T	C	1.11(0.90,1.36)	0.320	0.964
rs234785	*CBS*	G	C	0.92(0.77,1.09)	0.323	0.964
rs1801394	*MTRR*	A	G	1.09(0.92,1.29)	0.324	0.964
rs2077523	*ALDH1L1*	G	T	0.92(0.78,1.09)	0.325	0.964
rs3797535	*DMGDH*	T	C	1.17(0.86,1.60)	0.326	0.964
rs11849530	*MTHFD1*	G	A	0.91(0.75,1.10)	0.327	0.964
rs7937515	*FOLR3*	G	A	1.19(0.84,1.69)	0.327	0.964
rs12209517	*SLC22A3*	G	C	1.14(0.88,1.49)	0.329	0.964
rs9897362	*PEMT*	A	G	0.84(0.60,1.19)	0.329	0.964
rs2305795	*DNMT1*	G	A	0.92(0.79,1.09)	0.331	0.964
rs556808	*MTHFD2L*	C	T	0.85(0.61,1.18)	0.332	0.964
rs9383858	*MTHFD1L*	C	T	1.09(0.92,1.29)	0.335	0.964
rs12723350	*CTH*	C	T	1.19(0.83,1.70)	0.338	0.964
rs2236224	*MTHFD1*	T	C	1.09(0.92,1.29)	0.338	0.964
rs10514154	*DMGDH*	G	A	0.90(0.73,1.11)	0.339	0.964
rs12366105	*FOLR3*	C	T	1.08(0.92,1.28)	0.341	0.964
rs859101	*SLC44A3*	A	C	1.08(0.92,1.28)	0.342	0.964
rs9478934	*MTHFD1L*	G	A	1.19(0.83,1.69)	0.342	0.964
rs1109859	*PEMT*	C	T	0.90(0.73,1.12)	0.343	0.964
rs2445887	*DMGDH*	T	C	0.92(0.78,1.09)	0.343	0.964
rs129956	*SARDH*	C	T	0.85(0.62,1.19)	0.344	0.964
rs2286671	*PLD2*	C	T	1.09(0.92,1.29)	0.344	0.964
rs3744962	*TYMS*	C	T	1.15(0.86,1.54)	0.346	0.964
rs17080689	*MTHFD1L*	C	A	0.88(0.67,1.15)	0.347	0.964
rs3796349	*CHDH*	G	A	0.86(0.62,1.18)	0.347	0.964
rs4744533	*SARDH*	T	C	0.92(0.78,1.09)	0.347	0.964
rs12906758	*MTHFS*	A	T	1.11(0.90,1.37)	0.348	0.964
rs4676168	*SLC5A7*	T	C	0.92(0.77,1.10)	0.348	0.964
rs11634787	*MTHFS*	A	G	0.86(0.63,1.18)	0.349	0.964
rs131778	*CHKB*	T	C	0.93(0.79,1.09)	0.349	0.964
rs3818239	*MTHFD1*	G	A	0.88(0.68,1.15)	0.349	0.964
rs17597141	*CHKA*	C	G	0.91(0.74,1.12)	0.353	0.964
rs316025	*SLC22A2*	A	G	1.10(0.90,1.33)	0.353	0.964
rs6087988	*DNMT3B*	T	C	1.09(0.91,1.32)	0.353	0.964
rs6774437	*ALDH1L1*	C	A	0.93(0.79,1.09)	0.353	0.964
rs2481030	*SLC22A3*	G	A	0.92(0.77,1.10)	0.355	0.964
rs12638724	*ALDH1L1*	A	G	0.93(0.79,1.09)	0.359	0.964

RR: Risk ratio; **CI**: Confidence interval

SNP	Gene	Minor Allele	Major Allele	RR (95% CI)	P-value	Q-value
rs1800779	*NOS3*	G	A	0.93(0.78,1.09)	0.360	0.964
rs7236459	*TYMS*	G	A	1.14(0.86,1.50)	0.360	0.964
rs9889584	*PEMT*	A	G	0.86(0.62,1.19)	0.361	0.964
rs6669849	*SLC44A3*	T	C	1.20(0.81,1.80)	0.365	0.964
rs1256146	*MTHFD1*	A	G	1.10(0.90,1.35)	0.366	0.964
rs17824591	*MTHFD1*	A	G	0.91(0.74,1.12)	0.367	0.964
rs6910091	*MTHFD1L*	G	T	1.09(0.91,1.31)	0.369	0.964
rs696620	*SLC44A3*	C	T	1.08(0.92,1.27)	0.369	0.964
rs17080776	*MTHFD1L*	C	T	1.08(0.91,1.28)	0.370	0.964
rs10493570	*SLC44A5*	T	C	1.12(0.87,1.43)	0.374	0.964
rs859063	*SLC44A3*	A	G	0.93(0.78,1.10)	0.374	0.964
rs567754	*BHMT*	T	C	1.09(0.91,1.30)	0.375	0.964
rs6792030	*ALDH1L1*	C	T	1.10(0.89,1.36)	0.375	0.964
rs3774609	*CHDH*	G	T	0.93(0.79,1.09)	0.376	0.964
rs6745054	*MTHFD2*	C	T	0.91(0.73,1.13)	0.376	0.964
rs11627387	*MTHFD1*	A	G	0.92(0.77,1.10)	0.377	0.964
rs4920035	*CBS*	A	G	0.89(0.68,1.16)	0.377	0.964
rs9383551	*MTHFD1L*	C	T	1.16(0.84,1.60)	0.379	0.964
rs129940	*SARDH*	G	A	0.86(0.61,1.21)	0.382	0.964
rs316002	*SLC22A2*	T	C	0.90(0.72,1.14)	0.387	0.964
rs161871	*MTRR*	G	A	1.09(0.89,1.34)	0.388	0.964
rs11755633	*MTHFD1L*	G	A	1.11(0.87,1.42)	0.392	0.964
rs2838951	*SLC19A1*	G	C	1.08(0.91,1.28)	0.394	0.964
rs131749	*CHKB*	A	G	0.93(0.78,1.10)	0.395	0.964
rs11235451	*FOLR3*	A	T	1.08(0.91,1.28)	0.396	0.964
rs6919680	*MTHFD1L*	G	T	1.13(0.85,1.49)	0.396	0.964
rs10819309	*FPGS*	A	G	0.93(0.79,1.10)	0.398	0.964
rs3851059	*MAT1A*	A	G	0.93(0.77,1.11)	0.400	0.964
rs957903	*SLC44A1*	C	T	1.09(0.90,1.31)	0.401	0.964
rs17677908	*MAT1A*	G	A	0.90(0.70,1.15)	0.403	0.964
rs10195701	*SLC5A7*	C	T	1.10(0.88,1.38)	0.404	0.964
rs3972	*CBS*	T	C	1.11(0.87,1.41)	0.405	0.964
rs7763414	*MTHFD1L*	T	A	1.10(0.88,1.38)	0.405	0.964
rs17232682	*MTHFD2L*	C	T	0.90(0.71,1.15)	0.406	0.964
rs2071010	*FOLR1*	A	G	0.88(0.64,1.20)	0.413	0.964
rs4702506	*MTRR*	C	T	1.09(0.88,1.36)	0.414	0.964
rs3821466	*ALDH1L1*	T	C	0.93(0.78,1.11)	0.416	0.964
rs12999687	*DNMT3A*	T	G	1.07(0.91,1.26)	0.418	0.964
rs4244599	*PEMT*	G	A	0.93(0.79,1.10)	0.419	0.964
rs16853723	*ATIC*	C	T	0.91(0.71,1.15)	0.420	0.964
rs9975829	*GART*	G	A	1.07(0.90,1.27)	0.420	0.964
rs12987326	*DNMT3A*	G	A	1.07(0.91,1.27)	0.421	0.964
rs2177268	*AMT*	A	T	1.08(0.90,1.30)	0.422	0.964
rs4817579	*GART*	T	C	1.07(0.90,1.28)	0.424	0.964
rs4819130	*SLC19A1*	C	T	0.93(0.79,1.11)	0.424	0.964
rs2073643	*SLC22A5*	T	C	0.94(0.79,1.10)	0.425	0.964
rs2847607	*TYMS*	A	G	1.09(0.89,1.32)	0.425	0.964
rs10874311	*SLC44A5*	T	C	1.08(0.90,1.29)	0.426	0.964
rs2987981	*MTHFD1*	C	T	0.93(0.76,1.12)	0.428	0.964
rs487637	*MTHFD1L*	G	T	1.08(0.90,1.29)	0.433	0.964
rs316020	*SLC22A2*	T	C	0.90(0.69,1.17)	0.438	0.964
rs2510234	*SARDH*	C	T	1.07(0.90,1.27)	0.440	0.964
rs3783731	*MTHFD1*	T	C	1.09(0.88,1.35)	0.440	0.964

RR: Risk ratio; **CI**: Confidence interval

SNP	Gene	Minor Allele	Major Allele	RR (95% CI)	P-value	Q-value
rs694821	*SARDH*	G	A	1.07(0.91,1.25)	0.440	0.964
rs4902278	*MTHFD1*	A	G	0.87(0.60,1.25)	0.442	0.964
rs617219	*BHMT*	C	A	1.07(0.90,1.27)	0.445	0.964
rs734693	*DNMT3A*	C	T	0.93(0.78,1.12)	0.446	0.964
rs9322301	*MTHFD1L*	C	T	1.07(0.90,1.26)	0.447	0.964
rs12652027	*MAT2B*	C	T	1.16(0.79,1.71)	0.449	0.964
rs10987742	*FPGS*	T	C	0.92(0.75,1.14)	0.451	0.964
rs2073064	*MTHFD1L*	G	A	0.92(0.73,1.15)	0.451	0.964
rs2163005	*MTHFS*	G	A	1.07(0.90,1.26)	0.452	0.964
rs9397032	*MTHFD1L*	T	G	0.94(0.80,1.11)	0.454	0.964
rs2076828	*SLC22A3*	G	C	0.94(0.80,1.11)	0.457	0.964
rs9869368	*PLD1*	G	A	1.09(0.87,1.38)	0.457	0.964
rs17102596	*MAT1A*	C	T	0.92(0.75,1.14)	0.459	0.964
rs17269265	*SLC5A7*	G	A	1.08(0.88,1.33)	0.459	0.964
rs7544408	*SLC44A5*	C	G	0.94(0.79,1.11)	0.459	0.964
rs12995245	*DNMT3A*	C	T	1.06(0.90,1.25)	0.460	0.964
rs1476413	*MTHFR*	A	G	1.08(0.89,1.31)	0.460	0.964
rs17823744	*DMGDH*	G	A	1.11(0.85,1.44)	0.460	0.964
rs1045020	*SLC22A5*	T	C	1.10(0.85,1.44)	0.461	0.964
rs555671	*CTH*	T	C	0.88(0.63,1.24)	0.461	0.964
rs17622208	*SLC22A5*	A	G	1.07(0.90,1.26)	0.464	0.964
rs1051266	*SLC19A1*	A	G	0.94(0.79,1.11)	0.470	0.964
rs523230	*TYMS*	C	T	1.07(0.89,1.28)	0.470	0.964
rs1788484	*CBS*	T	C	0.94(0.78,1.12)	0.471	0.964
rs2618372	*DHFR*	A	C	1.07(0.89,1.28)	0.471	0.964
rs17535909	*MAT2B*	A	G	0.94(0.79,1.12)	0.472	0.964
rs4979631	*SARDH*	A	G	0.94(0.79,1.12)	0.472	0.964
rs624249	*SLC22A2*	A	C	0.94(0.79,1.12)	0.472	0.964
rs7946	*PEMT*	C	T	1.07(0.89,1.29)	0.472	0.964
rs1643638	*DHFR*	C	T	1.07(0.89,1.28)	0.473	0.964
rs9478908	*MTHFD1L*	G	A	0.93(0.77,1.13)	0.473	0.964
rs10494126	*CEPT1*	A	C	1.10(0.85,1.42)	0.474	0.964
rs273915	*SLC22A4*	C	G	0.94(0.78,1.12)	0.474	0.964
rs859096	*SLC44A3*	C	A	0.94(0.78,1.12)	0.474	0.964
rs12344130	*SLC44A1*	T	G	0.90(0.67,1.21)	0.475	0.964
rs13306567	*MTHFR*	C	G	1.15(0.78,1.69)	0.476	0.964
rs1643650	*DHFR*	C	T	1.07(0.89,1.28)	0.476	0.964
rs1051319	*CBS*	G	C	1.10(0.85,1.41)	0.477	0.964
rs1571511	*MTHFD1*	G	A	0.93(0.76,1.14)	0.477	0.964
rs10484779	*MTHFD1L*	G	T	0.92(0.73,1.16)	0.481	0.964
rs2072197	*TCN2*	A	C	0.92(0.73,1.16)	0.481	0.964
rs12743566	*SLC44A5*	G	A	1.11(0.83,1.50)	0.482	0.964
rs17184211	*MTRR*	T	A	0.93(0.76,1.14)	0.483	0.964
rs538017	*MTHFD1L*	C	T	1.07(0.89,1.28)	0.484	0.964
rs6860806	*SLC22A4*	A	G	0.94(0.80,1.11)	0.484	0.964
rs3912161	*SLC22A2*	G	A	1.12(0.81,1.56)	0.486	0.964
rs4629694	*MTHFD1L*	C	T	1.19(0.73,1.95)	0.486	0.964
rs4820887	*TCN2*	A	G	0.91(0.69,1.20)	0.488	0.964
rs1256142	*MTHFD1*	C	T	1.06(0.90,1.24)	0.493	0.964
rs647370	*FOLH1*	A	G	0.94(0.77,1.13)	0.493	0.964
rs10857859	*CEPT1*	C	G	1.06(0.89,1.27)	0.495	0.964
rs11908960	*FTCD*	C	T	0.92(0.73,1.17)	0.496	0.964
rs3764897	*PLD2*	T	C	1.08(0.86,1.36)	0.496	0.964

RR: Risk ratio; **CI**: Confidence interval

SNP	Gene	Minor Allele	Major Allele	RR (95% CI)	P-value	Q-value
rs4846052	*MTHFR*	T	C	0.94(0.80,1.12)	0.496	0.964
rs558936	*MTHFD1L*	A	G	0.94(0.78,1.13)	0.496	0.964
rs272894	*SLC22A4*	G	A	0.94(0.80,1.12)	0.499	0.964
rs3849308	*SLC44A3*	G	A	0.94(0.79,1.12)	0.500	0.964
rs17096504	*SLC44A5*	A	G	1.13(0.79,1.64)	0.501	0.964
rs10854479	*FTCD*	C	T	0.94(0.78,1.13)	0.502	0.964
rs16879258	*MTRR*	A	C	1.09(0.85,1.39)	0.502	0.964
rs13161245	*DHFR*	G	A	1.06(0.89,1.28)	0.503	0.964
rs1478834	*DHFR*	A	C	1.06(0.89,1.28)	0.503	0.964
rs711352	*PEMT*	C	G	1.07(0.88,1.29)	0.504	0.964
rs6087983	*DNMT3B*	T	G	1.08(0.87,1.33)	0.506	0.964
rs7638797	*PCYT1A*	C	A	1.06(0.90,1.25)	0.506	0.964
rs11155773	*MTHFD1L*	A	G	0.94(0.78,1.13)	0.507	0.964
rs12121543	*MTHFR*	A	C	1.07(0.88,1.30)	0.507	0.964
rs729352	*MAT2B*	T	C	1.06(0.89,1.28)	0.507	0.964
rs803422	*MTHFD1L*	T	C	1.07(0.89,1.28)	0.507	0.964
rs9432596	*SLC44A3*	A	G	1.07(0.87,1.31)	0.507	0.964
rs327588	*MTRR*	C	G	1.08(0.87,1.34)	0.508	0.964
rs7830	*NOS3*	A	C	1.06(0.89,1.25)	0.509	0.964
rs274567	*SLC22A5*	A	G	0.95(0.80,1.12)	0.511	0.964
rs1548362	*SARDH*	C	T	0.94(0.78,1.13)	0.513	0.964
rs6672579	*SLC44A5*	A	G	1.06(0.90,1.24)	0.514	0.964
rs9267649	*SLC44A4*	A	G	1.08(0.86,1.35)	0.514	0.964
rs11235466	*FOLR2*	C	T	0.90(0.65,1.24)	0.516	0.964
rs13036246	*DNMT3A*	T	C	0.95(0.80,1.12)	0.516	0.964
rs175862	*MTHFD1L*	C	T	1.06(0.88,1.28)	0.516	0.964
rs2847149	*TYMS*	A	G	1.06(0.90,1.24)	0.516	0.964
rs2115540	*MTHFS*	T	C	0.95(0.80,1.12)	0.519	0.964
rs737953	*TCN2*	G	C	0.95(0.80,1.12)	0.520	0.964
rs11235441	*FOLR3*	A	G	0.87(0.56,1.35)	0.522	0.964
rs416158	*PLD1*	A	T	0.93(0.75,1.16)	0.522	0.964
rs582326	*SARDH*	G	C	1.06(0.89,1.26)	0.522	0.964
rs7639712	*ALDH1L1*	G	A	0.93(0.73,1.17)	0.522	0.964
rs1001761	*TYMS*	T	C	1.05(0.90,1.24)	0.523	0.964
rs1476331	*PCYT1A*	G	A	1.06(0.90,1.24)	0.524	0.964
rs2299648	*FOLH1*	A	G	1.06(0.89,1.26)	0.524	0.964
rs9644967	*SLC44A1*	A	G	1.06(0.89,1.25)	0.524	0.964
rs7712332	*DHFR*	G	A	1.06(0.89,1.26)	0.525	0.964
rs11880388	*DNMT1*	A	G	1.05(0.90,1.24)	0.526	0.964
rs2519154	*SARDH*	G	A	1.06(0.89,1.25)	0.526	0.964
rs162029	*MTRR*	A	G	1.07(0.88,1.30)	0.527	0.964
rs497161	*MTHFD1L*	A	G	0.95(0.80,1.12)	0.527	0.964
rs2277820	*FTCD*	T	C	0.94(0.78,1.13)	0.528	0.964
rs315996	*SLC22A2*	A	G	0.92(0.72,1.18)	0.529	0.964
rs2241553	*CHPT1*	C	A	0.94(0.79,1.13)	0.530	0.964
rs2297291	*SLC19A1*	A	G	0.95(0.80,1.12)	0.531	0.964
rs3789699	*SLC44A3*	C	T	0.92(0.70,1.20)	0.531	0.964
rs1868138	*ALDH1L1*	T	A	1.06(0.88,1.29)	0.533	0.964
rs2502741	*SARDH*	G	A	0.95(0.81,1.11)	0.533	0.964
rs3087896	*PCYT1A*	T	C	1.08(0.84,1.40)	0.535	0.964
rs7737937	*SLC22A4*	A	G	0.93(0.74,1.17)	0.535	0.964
rs3760183	*PEMT*	T	G	1.09(0.84,1.40)	0.536	0.964
rs2073067	*MTHFD1L*	C	G	1.06(0.89,1.26)	0.537	0.964

RR: Risk ratio; **CI**: Confidence interval

SNP	Gene	Minor Allele	Major Allele	RR (95% CI)	P-value	Q-value
rs13306560	*MTHFR*	A	G	1.13(0.77,1.66)	0.539	0.964
rs4646767	*ALDH1L1*	T	C	0.95(0.81,1.12)	0.539	0.964
rs6502823	*PLD2*	T	C	0.91(0.68,1.23)	0.539	0.964
rs162031	*MTRR*	T	C	1.07(0.86,1.32)	0.540	0.964
rs2839947	*MTHFD1L*	C	T	1.06(0.89,1.25)	0.540	0.964
rs3816556	*DNMT1*	C	G	0.94(0.79,1.14)	0.541	0.964
rs12634587	*PCYT1A*	G	C	0.94(0.79,1.14)	0.542	0.964
rs6902496	*MTHFD1L*	T	C	0.94(0.77,1.15)	0.545	0.964
rs2275122	*CEPT1*	C	A	1.09(0.83,1.42)	0.546	0.964
rs4646398	*PEMT*	G	C	1.10(0.80,1.52)	0.546	0.964
rs2838950	*SLC19A1*	T	C	0.94(0.77,1.15)	0.547	0.964
rs2516557	*CHKB*	A	G	1.10(0.80,1.51)	0.550	0.964
rs3850181	*PLD1*	A	G	1.10(0.81,1.50)	0.550	0.964
rs2073191	*MTHFD1L*	G	A	0.94(0.78,1.14)	0.551	0.964
rs17097955	*SLC44A5*	C	T	1.11(0.79,1.56)	0.553	0.964
rs7173671	*MTHFS*	A	G	0.95(0.80,1.13)	0.553	0.964
rs859106	*SLC44A3*	C	A	0.93(0.73,1.19)	0.553	0.964
rs3776455	*MTRR*	G	A	1.06(0.88,1.26)	0.554	0.964
rs2236479	*SLC19A1*	A	G	1.05(0.89,1.25)	0.555	0.964
rs4846049	*MTHFR*	T	G	1.06(0.88,1.26)	0.555	0.964
rs17230459	*MTHFD2L*	T	C	1.07(0.86,1.32)	0.556	0.964
rs2043305	*SLC44A2*	T	C	1.06(0.87,1.30)	0.556	0.964
rs1563632	*SHMT1*	C	T	0.95(0.79,1.13)	0.558	0.964
rs96525	*DMGDH*	T	C	0.94(0.76,1.16)	0.558	0.964
rs10518120	*MTHFD2L*	G	A	1.07(0.86,1.32)	0.561	0.964
rs2853532	*TYMS*	T	C	1.05(0.89,1.25)	0.562	0.964
rs653753	*SLC22A2*	C	G	1.07(0.84,1.37)	0.562	0.964
rs7177659	*MTHFS*	A	C	0.95(0.81,1.12)	0.563	0.964
rs12122907	*SLC44A5*	A	G	1.07(0.86,1.32)	0.564	0.964
rs13428812	*DNMT3A*	G	A	0.95(0.80,1.13)	0.564	0.964
rs4676169	*SLC5A7*	G	A	0.95(0.81,1.13)	0.564	0.964
rs3827752	*SLC44A3*	C	A	1.08(0.84,1.38)	0.566	0.964
rs157572	*SLC22A4*	C	G	1.05(0.88,1.26)	0.567	0.964
rs9293761	*DMGDH*	A	G	0.95(0.80,1.13)	0.568	0.964
rs10493879	*SLC44A3*	A	C	0.93(0.72,1.20)	0.569	0.964
rs11667630	*DNMT1*	A	C	1.05(0.89,1.24)	0.570	0.964
rs10925257	*MTR*	G	A	0.94(0.77,1.15)	0.571	0.964
rs13070856	*ALDH1L1*	A	G	0.95(0.79,1.14)	0.571	0.964
rs2839116	*FTCD*	C	A	1.05(0.88,1.26)	0.571	0.964
rs1956545	*MTHFD1*	G	A	1.09(0.80,1.50)	0.573	0.964
rs11724468	*MTHFD2L*	G	A	1.06(0.87,1.29)	0.574	0.964
rs1371795	*MTHFD2L*	G	A	0.95(0.80,1.13)	0.574	0.964
rs2073066	*MTHFD1L*	C	T	1.07(0.85,1.33)	0.574	0.964
rs1805087	*MTR*	G	A	0.94(0.77,1.15)	0.576	0.964
rs406193	*DNMT3B*	T	C	0.93(0.73,1.19)	0.577	0.964
rs10465165	*SARDH*	T	G	0.94(0.76,1.17)	0.580	0.964
rs11612037	*SHMT2*	T	C	1.11(0.77,1.60)	0.580	0.964
rs859057	*SLC44A3*	A	C	0.94(0.76,1.17)	0.580	0.964
rs859104	*SLC44A3*	G	C	1.05(0.89,1.24)	0.581	0.964
rs6676866	*MTR*	T	G	1.05(0.89,1.23)	0.582	0.964
rs6923486	*MTHFD1L*	A	G	0.94(0.75,1.18)	0.582	0.964
rs9325622	*CBS*	G	A	0.95(0.80,1.13)	0.586	0.964
rs817580	*CEPT1*	A	C	1.07(0.85,1.35)	0.587	0.964

RR: Risk ratio; **CI**: Confidence interval

SNP	Gene	Minor Allele	Major Allele	RR (95% CI)	P-value	Q-value
rs1868128	*ALDH1L1*	A	G	1.05(0.89,1.24)	0.588	0.964
rs3768139	*MTR*	G	C	1.05(0.89,1.24)	0.588	0.964
rs4659743	*MTR*	A	T	1.05(0.89,1.24)	0.588	0.964
rs11102218	*CEPT1*	G	A	1.05(0.89,1.23)	0.589	0.964
rs10802569	*MTR*	G	C	1.05(0.89,1.24)	0.590	0.964
rs10932608	*ATIC*	A	T	1.06(0.86,1.29)	0.590	0.964
rs7518629	*SLC44A5*	T	G	0.96(0.81,1.13)	0.592	0.964
rs859081	*SLC44A3*	T	C	0.95(0.77,1.16)	0.592	0.964
rs12137650	*SLC44A3*	T	C	0.95(0.80,1.14)	0.593	0.964
rs13307588	*NOS3*	A	G	0.91(0.63,1.31)	0.593	0.964
rs471547	*FOLR3*	G	T	1.10(0.79,1.53)	0.593	0.964
rs1058151	*TYMS*	G	A	0.96(0.81,1.13)	0.594	0.964
rs17349743	*MTHFD1L*	C	T	0.95(0.80,1.14)	0.596	0.964
rs7639752	*PCYT1A*	G	A	0.96(0.81,1.13)	0.596	0.964
rs10491810	*SLC44A1*	A	T	0.91(0.65,1.29)	0.597	0.964
rs1327873	*CTH*	C	G	0.93(0.70,1.23)	0.598	0.964
rs10887718	*MAT1A*	C	T	0.96(0.82,1.13)	0.600	0.964
rs588885	*CEPT1*	T	A	1.06(0.85,1.33)	0.602	0.964
rs1013940	*SLC5A7*	C	T	0.93(0.70,1.23)	0.603	0.964
rs1266164	*MTR*	A	G	1.05(0.88,1.24)	0.603	0.964
rs7631913	*PCYT1A*	T	C	0.96(0.81,1.13)	0.603	0.964
rs12661281	*SLC44A4*	A	T	1.06(0.84,1.34)	0.604	0.964
rs1575219	*MTHFD1L*	A	G	0.95(0.77,1.17)	0.604	0.964
rs13194204	*MTHFD1L*	A	G	1.09(0.79,1.51)	0.606	0.965
rs2114635	*SLC5A7*	G	A	1.04(0.89,1.23)	0.610	0.967
rs4924892	*PEMT*	C	T	1.06(0.85,1.32)	0.612	0.967
rs6795005	*ALDH1L1*	A	G	1.05(0.86,1.30)	0.613	0.967
rs681475	*CTH*	A	G	0.96(0.80,1.14)	0.613	0.967
rs7237413	*TYMS*	T	C	1.05(0.87,1.26)	0.613	0.967
rs1050993	*MTR*	A	G	1.05(0.88,1.24)	0.615	0.967
rs3099820	*MTHFD2*	T	C	1.06(0.85,1.32)	0.615	0.967
rs1771798	*MTHFD1L*	A	G	1.08(0.81,1.44)	0.616	0.967
rs10179195	*MAT2A*	G	A	1.04(0.88,1.23)	0.618	0.967
rs242542	*DNMT3B*	G	A	0.93(0.71,1.23)	0.619	0.967
rs9842910	*ALDH1L1*	A	G	1.05(0.86,1.30)	0.619	0.967
rs129934	*SARDH*	T	C	0.95(0.77,1.18)	0.625	0.973
rs2290480	*PLD1*	A	C	1.05(0.86,1.29)	0.627	0.973
rs2662314	*SLC22A4*	T	C	1.06(0.84,1.34)	0.627	0.973
rs3737967	*MTHFR*	T	C	0.90(0.60,1.36)	0.629	0.973
rs731991	*TCN2*	G	A	0.96(0.82,1.13)	0.629	0.973
rs7176987	*MTHFS*	C	A	0.95(0.76,1.18)	0.633	0.974
rs657801	*CEPT1*	C	T	0.96(0.80,1.14)	0.634	0.974
rs2275566	*MTR*	C	T	1.04(0.88,1.23)	0.637	0.974
rs2839111	*FTCD*	T	C	0.95(0.78,1.16)	0.637	0.974
rs803470	*MTHFD1L*	A	G	0.94(0.74,1.20)	0.637	0.974
rs7636149	*PCYT1A*	A	G	1.04(0.88,1.23)	0.639	0.974
rs2275565	*MTR*	A	C	0.96(0.79,1.16)	0.640	0.974
rs13212656	*MTHFD1L*	G	C	0.95(0.74,1.20)	0.642	0.974
rs1889037	*SLC44A5*	G	C	1.04(0.88,1.23)	0.643	0.974
rs2853533	*TYMS*	C	G	1.05(0.84,1.32)	0.644	0.974
rs3768142	*MTR*	G	T	1.04(0.88,1.23)	0.645	0.974
rs4073394	*FOLR3*	G	A	1.04(0.88,1.24)	0.645	0.974
rs7175620	*MTHFS*	C	T	1.05(0.87,1.26)	0.647	0.974

RR: Risk ratio; **CI**: Confidence interval

SNP	Gene	Minor Allele	Major Allele	RR (95% CI)	P-value	Q-value
rs11965547	*SLC44A4*	A	G	1.07(0.81,1.40)	0.648	0.974
rs4820886	*TCN2*	G	T	0.94(0.73,1.22)	0.648	0.974
rs11950562	*SLC22A4*	C	A	1.04(0.88,1.23)	0.649	0.974
rs16853826	*ATIC*	A	G	1.06(0.84,1.33)	0.651	0.974
rs17751556	*MTHFD1*	C	T	0.93(0.68,1.27)	0.651	0.974
rs5749131	*TCN2*	A	G	1.04(0.88,1.23)	0.652	0.974
rs17272671	*FTCD*	C	T	1.05(0.84,1.31)	0.653	0.974
rs12483377	*SLC19A1*	A	G	1.07(0.80,1.41)	0.655	0.974
rs4646754	*ALDH1L1*	T	C	0.96(0.81,1.14)	0.657	0.974
rs859088	*SLC44A3*	T	C	0.96(0.80,1.15)	0.657	0.974
rs17579604	*SLC44A3*	G	A	0.95(0.77,1.18)	0.658	0.974
rs3747003	*FTCD*	T	C	0.96(0.80,1.15)	0.658	0.974
rs13002567	*DNMT3A*	C	T	1.04(0.86,1.26)	0.659	0.974
rs437302	*DNMT3B*	A	G	0.94(0.71,1.25)	0.660	0.974
rs10181373	*SLC5A7*	A	C	0.96(0.80,1.15)	0.663	0.978
rs2307116	*MTRR*	T	C	0.96(0.80,1.15)	0.667	0.981
rs6940322	*MTHFD1L*	T	A	0.96(0.81,1.14)	0.668	0.981
rs2236222	*MTHFD1*	C	T	0.94(0.70,1.26)	0.669	0.981
rs466791	*CBS*	T	C	0.95(0.75,1.21)	0.673	0.984
rs1571983	*SLC44A5*	C	T	0.96(0.81,1.15)	0.676	0.984
rs474244	*SLC22A2*	T	C	1.04(0.86,1.26)	0.677	0.984
rs1885031	*MTHFD1*	G	A	0.94(0.71,1.25)	0.679	0.984
rs402894	*CBS*	C	T	1.04(0.86,1.25)	0.679	0.984
rs616827	*SLC44A5*	G	T	1.04(0.87,1.25)	0.679	0.984
rs11911976	*CBS*	C	T	0.96(0.81,1.15)	0.680	0.984
rs3754255	*MTR*	T	C	1.04(0.88,1.22)	0.680	0.984
rs181715	*PLD1*	A	T	0.97(0.81,1.15)	0.683	0.984
rs3849303	*SLC44A3*	T	C	0.95(0.75,1.21)	0.683	0.984
rs1770449	*MTR*	G	A	1.04(0.87,1.23)	0.684	0.984
rs12211869	*MTHFD1L*	T	G	0.96(0.81,1.15)	0.688	0.984
rs6058896	*DNMT3B*	T	C	1.08(0.75,1.54)	0.688	0.984
rs688120	*CEPT1*	A	T	0.97(0.81,1.15)	0.690	0.984
rs1072389	*MTHFD2L*	A	G	0.97(0.81,1.15)	0.692	0.984
rs1263781	*CHPT1*	T	A	0.97(0.82,1.14)	0.692	0.984
rs234706	*CBS*	A	G	1.04(0.87,1.24)	0.692	0.984
rs6923669	*MTHFD1L*	G	A	1.05(0.83,1.32)	0.695	0.984
rs3764899	*PLD2*	T	C	0.97(0.81,1.15)	0.697	0.984
rs13183229	*MTRR*	A	G	0.97(0.82,1.15)	0.700	0.984
rs16961114	*SHMT1*	C	G	0.96(0.80,1.17)	0.701	0.984
rs162024	*MTRR*	G	T	0.97(0.82,1.14)	0.703	0.984
rs2844458	*SLC44A4*	T	G	1.03(0.87,1.22)	0.704	0.984
rs10991622	*SLC44A1*	C	T	0.92(0.60,1.42)	0.705	0.984
rs11235468	*FOLR2*	G	T	1.05(0.82,1.34)	0.705	0.984
rs1249837	*SLC44A5*	A	G	1.03(0.87,1.22)	0.705	0.984
rs11155760	*MTHFD1L*	T	A	1.04(0.87,1.24)	0.706	0.984
rs10158990	*SLC44A5*	G	C	0.97(0.82,1.14)	0.707	0.984
rs328006	*SLC44A1*	C	G	1.05(0.80,1.39)	0.709	0.984
rs2330183	*SLC19A1*	C	T	0.97(0.82,1.15)	0.710	0.984
rs9332	*MTRR*	T	C	1.05(0.82,1.34)	0.710	0.984
rs5753220	*TCN2*	C	T	0.97(0.80,1.16)	0.713	0.984
rs2490334	*CEPT1*	A	G	0.97(0.81,1.15)	0.715	0.984
rs859074	*SLC44A3*	T	C	1.03(0.87,1.23)	0.716	0.984
rs9840089	*PCYT1A*	G	A	0.97(0.82,1.15)	0.716	0.984

RR: Risk ratio; **CI**: Confidence interval

SNP	Gene	Minor Allele	Major Allele	RR (95% CI)	P-value	Q-value
rs17226802	*BHMT2*	C	A	1.09(0.68,1.75)	0.717	0.984
rs2427988	*SARDH*	T	C	0.95(0.74,1.23)	0.717	0.984
rs83615	*PLD1*	G	A	0.96(0.77,1.20)	0.718	0.984
rs4451422	*FPGS*	C	A	1.03(0.87,1.22)	0.719	0.984
rs316171	*SLC22A3*	T	G	0.97(0.82,1.15)	0.721	0.984
rs4934027	*MAT1A*	T	C	0.97(0.79,1.17)	0.722	0.984
rs2427995	*SARDH*	T	G	0.95(0.71,1.27)	0.723	0.984
rs3820571	*MTR*	G	T	1.03(0.87,1.22)	0.724	0.984
rs83616	*PLD1*	G	A	1.03(0.87,1.22)	0.724	0.984
rs7686861	*MTHFD2L*	C	T	1.03(0.87,1.22)	0.725	0.984
rs4573897	*MTHFS*	A	G	1.03(0.87,1.22)	0.727	0.984
rs6799991	*ALDH1L1*	A	G	1.03(0.87,1.21)	0.727	0.984
rs2619268	*SLC22A2*	A	C	0.97(0.80,1.17)	0.728	0.984
rs2839127	*FTCD*	A	G	1.04(0.84,1.30)	0.728	0.984
rs9901160	*SHMT1*	A	G	0.96(0.77,1.20)	0.728	0.984
rs2586167	*MTHFS*	T	C	0.97(0.81,1.16)	0.729	0.984
rs803447	*MTHFD1L*	T	C	0.97(0.83,1.14)	0.729	0.984
rs7552892	*SLC44A3*	T	C	0.96(0.77,1.21)	0.736	0.988
rs2298444	*FOLR2*	G	A	0.97(0.79,1.18)	0.737	0.988
rs2073836	*SARDH*	A	T	1.03(0.87,1.23)	0.739	0.988
rs2850146	*CBS*	G	C	0.95(0.71,1.28)	0.739	0.988
rs162899	*SLC22A4*	G	A	0.97(0.81,1.16)	0.743	0.988
rs3790715	*CEPT1*	C	T	0.96(0.74,1.24)	0.743	0.988
rs11892646	*DNMT3A*	T	C	1.04(0.82,1.33)	0.745	0.988
rs10515456	*SLC22A5*	A	G	1.05(0.79,1.38)	0.747	0.988
rs6464119	*NOS3*	T	C	0.97(0.79,1.19)	0.748	0.988
rs333216	*SLC5A7*	T	C	0.97(0.81,1.17)	0.751	0.988
rs614549	*SLC44A4*	C	T	1.03(0.87,1.21)	0.752	0.988
rs7715062	*MTRR*	T	G	0.97(0.82,1.15)	0.752	0.988
rs11656215	*PEMT*	T	C	1.03(0.87,1.21)	0.753	0.988
rs7280485	*FTCD*	A	G	1.03(0.86,1.23)	0.753	0.988
rs2283125	*SARDH*	A	C	1.03(0.86,1.23)	0.754	0.988
rs3772423	*ALDH1L1*	A	C	0.97(0.79,1.18)	0.754	0.988
rs9371494	*MTHFD1L*	G	A	1.03(0.86,1.23)	0.754	0.988
rs6668344	*MTR*	T	C	1.03(0.87,1.21)	0.755	0.988
rs10026687	*MTHFD2L*	C	T	1.03(0.84,1.26)	0.758	0.988
rs10887721	*MAT1A*	C	G	1.04(0.82,1.31)	0.758	0.988
rs2303629	*CHPT1*	G	C	0.97(0.82,1.16)	0.759	0.988
rs17004785	*SLC19A1*	C	G	1.04(0.81,1.34)	0.761	0.988
rs1738575	*MTHFD1L*	G	C	0.98(0.83,1.15)	0.762	0.988
rs2073833	*SARDH*	G	C	1.03(0.87,1.21)	0.767	0.988
rs10874305	*SLC44A5*	T	C	1.03(0.85,1.26)	0.768	0.988
rs12175302	*MTHFD1L*	C	G	1.04(0.79,1.38)	0.768	0.988
rs6087982	*DNMT3B*	G	A	1.03(0.85,1.25)	0.769	0.988
rs17780078	*CHPT1*	A	G	1.06(0.72,1.55)	0.774	0.988
rs13089568	*ALDH1L1*	A	G	1.02(0.87,1.20)	0.775	0.988
rs190024	*SLC44A5*	C	A	1.03(0.84,1.26)	0.775	0.988
rs4855877	*AMT*	G	A	0.98(0.83,1.15)	0.775	0.988
rs2510257	*SARDH*	A	C	1.03(0.85,1.25)	0.776	0.988
rs11924478	*ALDH1L1*	T	C	1.03(0.85,1.24)	0.777	0.988
rs706209	*CBS*	T	C	0.98(0.83,1.16)	0.777	0.988
rs16988828	*TCN2*	G	A	0.96(0.74,1.25)	0.778	0.988
rs3826785	*DNMT1*	T	C	1.04(0.81,1.33)	0.778	0.988

RR: Risk ratio; **CI**: Confidence interval

SNP	Gene	Minor Allele	Major Allele	RR (95% CI)	P-value	Q-value
rs502396	*TYMS*	C	T	1.02(0.87,1.20)	0.779	0.988
rs7281816	*FTCD*	T	C	0.97(0.76,1.23)	0.779	0.988
rs10196635	*DNMT3A*	T	A	1.04(0.79,1.37)	0.780	0.988
rs2586181	*MTHFS*	T	C	1.04(0.80,1.35)	0.780	0.988
rs4659723	*MTR*	T	C	0.97(0.76,1.23)	0.780	0.988
rs6009931	*CHKB*	G	T	0.96(0.69,1.32)	0.780	0.988
rs4869984	*MTHFD1L*	T	C	1.02(0.87,1.21)	0.781	0.988
rs3819255	*CHKA*	A	T	0.98(0.82,1.16)	0.784	0.988
rs12565150	*SLC44A3*	A	T	0.97(0.79,1.19)	0.785	0.988
rs2839121	*FTCD*	G	C	0.97(0.79,1.20)	0.786	0.988
rs12661373	*MTHFD1L*	A	G	1.03(0.85,1.24)	0.788	0.988
rs2424898	*DNMT3B*	C	T	1.03(0.85,1.24)	0.788	0.988
rs828863	*MTHFD2*	A	G	1.04(0.77,1.41)	0.788	0.988
rs2230491	*MTHFD1*	T	C	1.03(0.81,1.32)	0.789	0.988
rs11751336	*MTHFD1L*	C	G	0.95(0.66,1.37)	0.793	0.992
rs634841	*MTHFS*	T	C	1.03(0.83,1.29)	0.795	0.993
rs11587108	*SLC44A3*	T	C	1.03(0.83,1.27)	0.797	0.994
rs16837183	*ALDH1L1*	C	T	0.95(0.64,1.41)	0.799	0.995
rs7560488	*DNMT3A*	C	T	1.02(0.87,1.21)	0.800	0.995
rs1076504	*PLD1*	G	C	1.03(0.84,1.25)	0.801	0.995
rs8128028	*CBS*	T	C	0.98(0.82,1.17)	0.803	0.995
rs7769613	*MTHFD1L*	A	G	0.98(0.80,1.20)	0.805	0.995
rs7349940	*MTHFD1L*	A	T	0.97(0.75,1.25)	0.807	0.995
rs12202291	*MTHFD1L*	G	A	0.98(0.82,1.17)	0.809	0.995
rs10066017	*MTRR*	G	T	1.02(0.85,1.23)	0.812	0.995
rs11165263	*SLC44A3*	C	T	0.98(0.80,1.20)	0.813	0.995
rs7700970	*BHMT*	T	C	1.02(0.85,1.23)	0.817	0.995
rs4979632	*SARDH*	T	C	1.02(0.84,1.24)	0.818	0.995
rs12205664	*MTHFD1L*	T	C	1.05(0.71,1.55)	0.819	0.995
rs6271	*SARDH*	T	C	1.04(0.75,1.43)	0.820	0.995
rs6446976	*MTHFD2L*	C	G	0.96(0.68,1.36)	0.820	0.995
rs2057519	*SLC44A5*	G	A	0.98(0.83,1.16)	0.822	0.995
rs7594432	*DNMT3A*	C	T	0.98(0.83,1.16)	0.823	0.995
rs17567259	*SLC44A5*	G	A	1.04(0.72,1.52)	0.824	0.995
rs881883	*CHDH*	C	T	1.03(0.81,1.29)	0.824	0.995
rs10483080	*SLC19A1*	G	C	1.03(0.81,1.31)	0.825	0.995
rs9974320	*FTCD*	A	G	1.02(0.85,1.23)	0.826	0.995
rs175864	*MTHFD1L*	A	C	0.97(0.71,1.31)	0.829	0.995
rs9978174	*FTCD*	C	G	0.98(0.83,1.17)	0.831	0.995
rs2733088	*MTHFS*	A	G	0.98(0.83,1.16)	0.833	0.995
rs6586282	*CBS*	T	C	1.03(0.82,1.29)	0.833	0.995
rs7238	*CHKB*	C	T	0.97(0.74,1.27)	0.833	0.995
rs9606756	*TCN2*	G	A	0.97(0.76,1.24)	0.834	0.995
rs2342309	*PCYT1A*	T	C	0.98(0.82,1.18)	0.835	0.995
rs316029	*SLC22A2*	T	C	0.97(0.76,1.25)	0.835	0.995
rs559088	*DMGDH*	C	G	1.02(0.86,1.21)	0.836	0.995
rs575341	*FOLR3*	A	G	0.98(0.76,1.25)	0.839	0.995
rs6775861	*PCYT1A*	T	C	1.04(0.74,1.45)	0.842	0.995
rs6557111	*MTHFD1L*	A	G	1.02(0.85,1.22)	0.845	0.995
rs77905	*SARDH*	T	C	1.02(0.86,1.20)	0.846	0.995
rs11203172	*CBS*	T	G	1.02(0.82,1.28)	0.847	0.995
rs13194929	*MTHFD1L*	G	A	1.02(0.84,1.24)	0.849	0.995
rs35020344	*MTHFD1*	G	A	1.02(0.86,1.20)	0.850	0.995

RR: Risk ratio; **CI**: Confidence interval

SNP	Gene	Minor Allele	Major Allele	RR (95% CI)	P-value	Q-value
rs11953102	*DMGDH*	C	G	0.98(0.80,1.20)	0.855	0.995
rs2286670	*PLD2*	A	C	1.02(0.81,1.29)	0.859	0.995
rs13069815	*ALDH1L1*	A	C	0.98(0.74,1.29)	0.862	0.995
rs2073063	*MTHFD1L*	C	T	1.02(0.86,1.20)	0.863	0.995
rs1128162	*SLC46A1*	G	T	1.02(0.86,1.20)	0.864	0.995
rs182411	*SLC44A5*	A	G	0.98(0.81,1.19)	0.864	0.995
rs2164411	*DNMT3A*	T	C	0.98(0.79,1.21)	0.864	0.995
rs828858	*MTHFD2*	A	T	1.02(0.86,1.20)	0.865	0.995
rs1541332	*SARDH*	T	C	0.99(0.84,1.16)	0.866	0.995
rs853858	*DNMT3B*	A	G	1.01(0.86,1.19)	0.866	0.995
rs2242665	*SLC44A4*	G	A	0.99(0.84,1.16)	0.867	0.995
rs4869970	*MTHFD1L*	G	A	1.03(0.75,1.40)	0.867	0.995
rs859072	*SLC44A3*	G	A	0.98(0.80,1.21)	0.870	0.995
rs2993763	*MAT1A*	A	G	0.99(0.83,1.17)	0.871	0.995
rs6424386	*CTH*	A	T	0.98(0.76,1.26)	0.871	0.995
rs1045075	*PCYT1A*	T	C	0.99(0.84,1.17)	0.872	0.995
rs2073815	*SARDH*	C	T	1.01(0.86,1.19)	0.872	0.995
rs4659724	*MTR*	A	G	0.99(0.83,1.17)	0.873	0.995
rs933683	*DMGDH*	T	G	0.99(0.82,1.18)	0.874	0.995
rs161869	*MTRR*	T	C	1.01(0.86,1.20)	0.876	0.995
rs211688	*SLC44A5*	A	C	0.98(0.81,1.20)	0.877	0.995
rs7873937	*SLC44A1*	C	G	1.02(0.77,1.35)	0.877	0.995
rs2070578	*FTCD*	T	C	0.99(0.84,1.17)	0.878	0.995
rs4820874	*TCN2*	G	A	0.98(0.79,1.23)	0.878	0.995
rs4077829	*MTR*	T	G	0.99(0.84,1.17)	0.879	0.995
rs234709	*CBS*	T	C	1.01(0.85,1.20)	0.880	0.995
rs360402	*PLD1*	G	A	0.99(0.82,1.19)	0.883	0.995
rs4920037	*CBS*	A	G	1.01(0.83,1.25)	0.892	0.995
rs273909	*SLC22A4*	C	T	1.02(0.78,1.33)	0.893	0.995
rs7555627	*SLC44A5*	G	A	0.99(0.83,1.18)	0.893	0.995
rs12614943	*ATIC*	G	A	0.99(0.82,1.19)	0.894	0.995
rs2350631	*PEMT*	T	C	0.99(0.84,1.17)	0.894	0.995
rs4646745	*ALDH1L1*	T	C	0.99(0.81,1.21)	0.896	0.995
rs1052751	*PLD2*	A	G	1.02(0.81,1.27)	0.897	0.995
rs12941217	*PEMT*	A	G	1.01(0.85,1.20)	0.897	0.995
rs8118663	*DNMT3B*	G	A	0.99(0.82,1.20)	0.899	0.995
rs11676382	*MAT2A*	G	C	1.02(0.76,1.36)	0.900	0.995
rs2027963	*SARDH*	A	C	0.99(0.84,1.17)	0.901	0.995
rs381870	*SLC22A4*	T	A	1.01(0.83,1.24)	0.902	0.995
rs3788205	*SLC19A1*	T	C	1.01(0.84,1.22)	0.903	0.995
rs12626746	*FTCD*	T	C	0.99(0.84,1.17)	0.904	0.995
rs3815743	*MTRR*	G	A	1.01(0.82,1.26)	0.904	0.995
rs4819210	*FTCD*	A	G	0.99(0.82,1.20)	0.904	0.995
rs756682	*SARDH*	G	A	0.99(0.84,1.17)	0.904	0.995
rs12038630	*SLC44A3*	A	G	1.01(0.81,1.28)	0.905	0.995
rs6780561	*PLD1*	G	A	0.99(0.84,1.17)	0.905	0.995
rs3805673	*SLC22A4*	A	G	0.98(0.74,1.31)	0.906	0.995
rs478651	*DMGDH*	G	A	0.99(0.84,1.17)	0.906	0.995
rs10874314	*SLC44A5*	A	G	1.01(0.86,1.19)	0.907	0.995
rs685487	*MTHFS*	C	T	1.01(0.85,1.20)	0.907	0.995
rs3204635	*SHMT2*	T	C	0.99(0.82,1.19)	0.908	0.995
rs17112592	*SLC44A3*	G	A	1.01(0.83,1.24)	0.909	0.995
rs9478847	*MTHFD1L*	C	T	1.02(0.70,1.49)	0.909	0.995

RR: Risk ratio; **CI**: Confidence interval

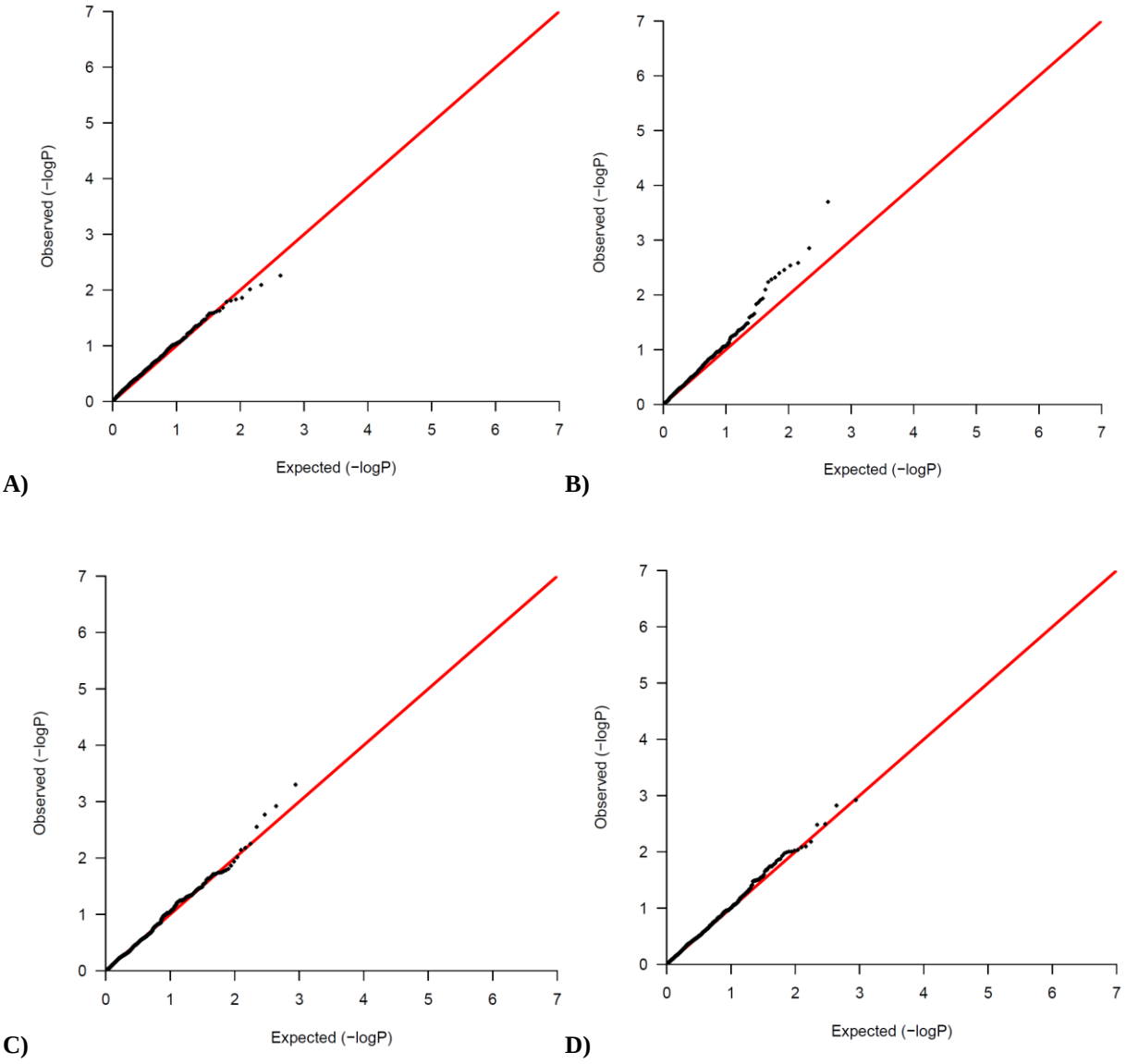
SNP	Gene	Minor Allele	Major Allele	RR (95% CI)	P-value	Q-value
rs12209109	*MTHFD1L*	C	T	0.99(0.83,1.18)	0.912	0.995
rs1611123	*SARDH*	A	G	0.99(0.84,1.17)	0.912	0.995
rs1789953	*CBS*	T	C	1.01(0.81,1.26)	0.917	0.995
rs7525338	*MTHFR*	T	C	0.94(0.28,3.18)	0.917	0.995
rs17719944	*SLC46A1*	G	A	1.02(0.75,1.38)	0.918	0.995
rs579283	*MTHFD1L*	T	C	0.99(0.84,1.17)	0.919	0.995
rs509474	*MTHFD1L*	C	G	0.99(0.84,1.17)	0.920	0.995
rs9322298	*MTHFD1L*	G	C	1.02(0.72,1.43)	0.920	0.995
rs328012	*SLC44A1*	G	T	0.99(0.82,1.20)	0.921	0.995
rs486416	*SLC44A4*	C	T	0.99(0.82,1.19)	0.921	0.995
rs506500	*BHMT*	T	C	1.01(0.84,1.21)	0.921	0.995
rs740234	*TCN2*	C	T	1.01(0.82,1.24)	0.922	0.995
rs1077872	*NOS3*	C	G	0.99(0.84,1.17)	0.923	0.995
rs7523188	*CTH*	G	A	0.99(0.81,1.21)	0.924	0.995
rs12773664	*MAT1A*	G	A	0.99(0.84,1.17)	0.925	0.995
rs524732	*MTHFD1L*	T	C	1.01(0.83,1.22)	0.925	0.995
rs672413	*DMGDH*	T	C	1.01(0.85,1.20)	0.925	0.995
rs7029443	*SLC44A1*	A	T	1.01(0.80,1.27)	0.925	0.995
rs162048	*MTRR*	G	A	0.99(0.78,1.25)	0.928	0.995
rs156110	*SLC22A4*	G	C	0.99(0.77,1.28)	0.930	0.995
rs943199	*SLC44A3*	G	T	0.99(0.83,1.19)	0.930	0.995
rs2289209	*CHDH*	A	G	0.99(0.70,1.38)	0.932	0.995
rs7757336	*SLC22A2*	G	T	1.01(0.80,1.28)	0.932	0.995
rs955516	*MTR*	A	T	0.99(0.84,1.17)	0.932	0.995
rs12129440	*MTR*	A	G	0.99(0.82,1.20)	0.933	0.995
rs3849306	*SLC44A3*	A	C	0.99(0.79,1.24)	0.933	0.995
rs1131603	*TCN2*	C	T	1.02(0.68,1.52)	0.936	0.995
rs6445607	*CHDH*	G	T	0.99(0.84,1.18)	0.936	0.995
rs10889869	*CTH*	A	G	1.01(0.74,1.39)	0.938	0.995
rs13050660	*FTCD*	T	C	0.99(0.83,1.19)	0.939	0.995
rs1593685	*SLC5A7*	G	C	0.99(0.74,1.32)	0.939	0.995
rs17407097	*SLC44A3*	G	A	1.01(0.80,1.27)	0.941	0.995
rs2241933	*PLD2*	T	G	1.01(0.84,1.20)	0.941	0.995
rs17292141	*FTCD*	G	A	1.01(0.75,1.37)	0.942	0.995
rs494620	*SLC44A4*	A	G	1.01(0.85,1.19)	0.944	0.995
rs11612551	*SHMT2*	A	G	1.01(0.84,1.21)	0.946	0.995
rs9874508	*ALDH1L1*	A	G	0.99(0.84,1.17)	0.946	0.995
rs12060570	*MTR*	C	G	1.00(0.84,1.18)	0.951	0.995
rs17112682	*SLC44A3*	G	A	1.01(0.72,1.43)	0.953	0.995
rs326123	*MTRR*	G	A	1.00(0.84,1.18)	0.953	0.995
rs316024	*SLC22A2*	A	G	1.01(0.84,1.20)	0.954	0.995
rs12053233	*MTHFD2*	T	C	1.01(0.84,1.21)	0.956	0.995
rs5997711	*TCN2*	T	C	1.00(0.84,1.18)	0.957	0.995
rs529087	*MTHFD1L*	T	C	1.01(0.83,1.22)	0.958	0.995
rs10925252	*MTR*	C	T	1.00(0.84,1.18)	0.959	0.995
rs12185084	*MTHFS*	A	G	1.00(0.81,1.22)	0.959	0.995
rs9804151	*CTH*	C	T	0.99(0.80,1.23)	0.959	0.995
rs12032960	*SLC44A3*	C	T	1.01(0.82,1.23)	0.960	0.995
rs4328397	*MTHFS*	C	T	1.01(0.79,1.28)	0.960	0.995
rs10493878	*SLC44A3*	G	A	0.99(0.80,1.24)	0.961	0.995
rs10778137	*CHPT1*	A	G	1.00(0.83,1.19)	0.961	0.995
rs2075798	*SLC44A4*	T	G	1.01(0.73,1.39)	0.962	0.995
rs9383552	*MTHFD1L*	G	A	1.01(0.72,1.41)	0.962	0.995

RR: Risk ratio; **CI**: Confidence interval

SNP	*Gene*	Minor Allele	Major Allele	RR (95% CI)	P-value	Q-value
rs10501409	*FOLR1*	C	A	1.01(0.78,1.31)	0.964	0.995
rs234784	*CBS*	T	C	1.00(0.85,1.19)	0.964	0.995
rs2612092	*TYMS*	A	G	0.99(0.76,1.30)	0.964	0.995
rs4646750	*ALDH1L1*	G	A	0.99(0.73,1.35)	0.964	0.995
rs12528219	*MTHFD1L*	C	G	1.00(0.78,1.28)	0.966	0.995
rs1806505	*MTR*	T	C	1.00(0.84,1.18)	0.969	0.995
rs3935460	*CHKA*	G	A	1.00(0.85,1.18)	0.971	0.995
rs803446	*MTHFD1L*	T	C	1.00(0.82,1.21)	0.972	0.995
rs162023	*MTRR*	A	G	1.00(0.85,1.17)	0.973	0.995
rs2293160	*PCYT1A*	C	T	1.00(0.84,1.19)	0.974	0.995
rs2297702	*CEPT1*	T	C	1.00(0.71,1.39)	0.974	0.995
rs762684	*MAT2A*	T	C	1.00(0.83,1.19)	0.974	0.995
rs17689550	*SLC22A5*	T	C	1.00(0.77,1.30)	0.976	0.995
rs380691	*DHFR*	C	T	1.00(0.84,1.19)	0.976	0.995
rs9982015	*CBS*	C	T	1.00(0.72,1.37)	0.976	0.995
rs2665355	*SLC22A3*	C	G	1.00(0.85,1.18)	0.977	0.995
rs1667627	*MTHFD2*	G	A	1.00(0.85,1.18)	0.979	0.995
rs9966612	*TYMS*	A	G	1.00(0.83,1.19)	0.980	0.995
rs585800	*BHMT*	T	A	1.00(0.83,1.21)	0.981	0.995
rs9478157	*MTHFD1L*	G	T	1.00(0.85,1.19)	0.981	0.995
rs3772431	*ALDH1L1*	A	G	1.00(0.84,1.18)	0.983	0.996
rs12134663	*MTHFR*	C	A	1.00(0.79,1.26)	0.984	0.996
rs333226	*SLC5A7*	G	A	1.00(0.79,1.27)	0.987	0.997
rs2502745	*SARDH*	C	G	1.00(0.85,1.18)	0.991	0.997
rs3733075	*CHDH*	T	C	1.00(0.85,1.18)	0.991	0.997
rs1801133	*MTHFR*	T	C	1.00(0.84,1.19)	0.992	0.997
rs698962	*SLC44A3*	A	G	1.00(0.82,1.23)	0.994	0.997
rs11082	*CHPT1*	G	A	1.00(0.85,1.18)	0.995	0.997
rs9432593	*SLC44A3*	G	A	1.00(0.83,1.21)	0.995	0.997
rs13212150	*MTHFD1L*	C	T	1.00(0.84,1.19)	0.996	0.997
rs2851391	*CBS*	T	C	1.00(0.85,1.18)	0.996	0.997
rs16948305	*TYMS*	T	C	1.00(0.79,1.27)	0.998	0.998
rs10918179	*RXRG*	A	C	1.00(0.84,1.19)	0.971	0.984
rs5750041	*ISX*	T	C	1.00(0.79,1.26)	0.971	0.984
rs11264527	*CRABP2*	C	T	1.00(0.84,1.20)	0.973	0.984
rs1154473	*ADH7*	T	C	1.00(0.85,1.18)	0.976	0.985
rs2012147	*ALDH1A2*	T	C	1.00(0.70,1.42)	0.982	0.989
rs7845956	*RDH10*	A	G	1.00(0.68,1.46)	0.99	0.994
rs1286773	*RARB*	G	C	1.00(0.79,1.26)	0.996	0.998
rs1128977	*RXRG*	T	C	1.00(0.84,1.19)	>0.999	>0.999

RR: Risk ratio; **CI**: Confidence interval

APPENDIX 5. QQ PLOTS



A) **B)**

C) **D)**

A) offspring vitamin A-related SNPs, **B)** maternal vitamin A-related SNPs, **C)** offspring folate and choline-related SNPs, **D)** maternal folate and choline-related SNPs

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