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## Candidate Genes and Risk for Cerebral Palsy: a Population-Based Study

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### Abstract

Studies suggest genetic polymorphisms may increase an individual's susceptibility to CP. Most findings have yet to be corroborated in an independent cohort. This case-control study is nested within all 334,333 infants  $\geq 36$  weeks gestation born at Kaiser Permanente Medical Care Program, 1991–2002. We included only non-Hispanic whites who had a neonatal blood sample available. Case patients (N=138) were identified from medical records to have spastic or dyskinetic CP. Controls (N=165) were randomly selected from the population. We genotyped polymorphisms previously associated with CP: inducible nitric oxide synthase (iNOS) -231, apolipoprotein E (apoE)  $\epsilon 2$  and  $\epsilon 4$  alleles, tumor necrosis factor- $\alpha$  -308, interleukin-8 -251, lymphotoxin 60, endothelial nitric oxide synthase -922, endothelial protein C receptor 219, mannose binding lectin 54 and 52, factor V Leiden, methyltetrahydrofolate reductase 1298 and 667, prothrombin 20210, and platelet activator inhibitor 11053. Similar to previous reports, the iNOS -231 T allele (25.7% vs. 18.9%,  $P=0.04$ ) and the apoE  $\epsilon 4$  allele (19.3% vs. 13.2%,  $P=0.04$ ) were more common in patients with CP than in controls. However, there was no statistically significant association between any genetic polymorphism and CP after correction for multiple comparisons.

### Introduction

Cerebral palsy (CP) is a group of non-progressive motor impairment syndromes caused by lesions of the brain arising early in development (1). The etiology of CP remains unclear in most cases. Alterations in genes involved in inflammation and coagulation have been implicated as risk factors for CP. Over 20 studies of CP have evaluated single nucleotide polymorphisms (SNPs) in genes that regulate the inflammatory and coagulation cascades, and polymorphisms in over 15 genes have been associated with CP (2–12). However, genetic association studies of CP have been hampered by multiple comparisons, small sample size and population heterogeneity, thus leading to inconsistent findings (3, 12–14).

A promoter region polymorphism in the interleukin-6 (IL-6) gene has been associated with CP both in Australia (4) and in our California population (5). The  $\epsilon 4$  allele of the apolipoprotein E (apoE) gene has also been associated with CP in more than one population

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(15, 16), though not all studies have supported this finding (17, 18). Few genetic studies of CP have been conducted in the US, and the majority of findings have yet to be corroborated in an independent cohort. Therefore, we set out to validate previously described genetic associations with CP, within a large California birth cohort of term and near-term infants.

## Methods

Our study population consists of all singleton live births  $\geq 36$  weeks gestation born between January 1, 1991 and December 31, 2002 in the Kaiser Permanente Medical Care Program (KPMCP), a large managed care organization. The members of KPMCP are demographically similar to the California population, except that the very poor and very wealthy are under-represented (19).

Children with CP were identified from the study population as previously reported (20). After electronically searching KPMCP records for physician diagnoses of “cerebral palsy”, “paresis” and “gait abnormality”, a single child neurologist (YW) reviewed medical records to confirm the diagnosis of CP. We defined CP as a non-progressive congenital motor dysfunction with examination findings of increased tone (spasticity, rigidity, dystonia) or choreoathetosis (21). Children with hypotonia, ataxia, myopathy, neural tube defect, genetic syndrome and chromosomal anomaly were excluded (22). We defined *mild* disability as minimal functional limitation; *moderate* disability as diminished use of the most affected limb; and *severe* disability as the lack of any functional use of the most affected limb (23).

### Case selection

To control for racial heterogeneity in SNP frequencies, our study included only non-Hispanic whites (referred to as “whites” in the remainder of the manuscript).

Of the 377 infants with CP identified in the birth cohort (20), we excluded 74 infants from the current study for the following reasons: brain malformation (39), resolution of motor abnormality by 3 years of age (24), unclear severity of CP (7), and congenital cytomegaloviral infection (4). Case infants whose newborn blood samples were unavailable for study (47), whose blood samples were taken after having received a blood transfusion (5), or whose blood samples were mislabeled (1), were also excluded. After excluding 112 non-whites, the remaining 138 *infants with CP* represent the cases in this study.

### Control selection

For the larger study, we randomly selected 652 control infants from the KPMCP birth cohort. Control infants with missing (64) or mislabeled (1) newborn blood samples were excluded. We were unable to genotype all control subjects due to financial constraints, and randomly excluded an additional 282 control infants. After excluding 140 nonwhites, the remaining 165 *infants* comprised the control group of this study.

### Blood sample collection

Stored neonatal blood specimens were retrieved from the newborn screening specimen archives maintained by the California Department of Public Health. Newborn blood specimens are collected on Guthrie card filter paper and allowed to dry at room temperature prior to submission for routine genetic and metabolic screening. Upon completion of the screening tests, remaining blood samples are stored at  $-15^{\circ}\text{C}$  in a single refrigerated warehouse.

Blood spot Guthrie cards were punched with a 3mm paper punch in a laminar flow hood under aseptic conditions. The Qiagen QIAamp blood kit #51161 (Valencia, CA) was used

for preparing genomic DNA from the blood spots. Two 3mm punches from each subject were placed into a 96-well plate and incubated at 56C for 1 hr in Qiagen buffer and Proteinase K enzyme from Amresco (Solon, Ohio). Quantitation of genomic DNA was performed using the Quant-iT™ DNA Assay Kit (24) (#Q33130) from Molecular Probes™ (Eugene, Oregon) with lambda DNA as a standard. PicoGreen® fluorescence was measured with a Synergy HT microplate reader (BIO-TEK®, Winooski, Vermont).

### Genotyping assays

All genotyping was performed blind to case status and clinical history. Commercial Applied Biosystems Taqman SNP probes (Foster City, California) were used to genotype single nucleotide polymorphisms (SNPs) using 0.5ng of genomic DNA (Table 1). We genotyped the following SNP's that have been previously associated with CP: tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) -308 (rs1800629) (8), interleukin-8 (IL-8) -251 (rs4073) (6), lymphotoxin 60 (rs1041981) (6, 11), endothelial nitric oxide synthase (eNOS) -922 (rs1800779) (11), inducible nitric oxide synthase (iNOS) -231 (rs1137933) (6), endothelial protein C receptor (EPCR) 219 (rs867186) (6), mannose binding lectin (MBL) 54 (rs1800450) and 52 (rs5030737) (8), factor V Leiden (FVL) 506 (rs6025) (10), methyltetrahydrofolate reductase (MTHFR) 1298 (rs1801131) and 667 (rs1801133) (10), prothrombin 20210 (rs1799963) (10), platelet activator inhibitor (PAI-1) 11053 (rs7242) (11), and apolipoprotein E (apo E) E2 and E4 alleles (rs429358 and rs7412) (15, 16, 18). The IL-6 -174 polymorphism was previously studied in this population (5), and therefore was not included in the current study.

Standard Taqman PCR reactions were performed using an Applied Biosystems 7500 Fast system AB 96-well optical plates (plates P/N 4366932). The reactions were designed according to the Applied Biosystems SNP assay protocol in 10 $\mu$ L volumes. Each reaction was done in a single well due to limited amounts of genomic DNA. Results from all experiments were obtained from Applied Biosystems SDS software v2.0 and Copy Caller software v1.0.

### Data analysis

We defined SNP genotypes as follows: common homozygote = 2 copies of the common allele; heterozygote = one copy of each allele; and rare homozygote = 2 copies of the rare allele. The goal of this study was to replicate previously reported genetic associations with CP. Therefore, using logistic regression, we determined odds ratios (OR) and 95% confidence intervals (CI) using the three genetic comparisons that were most commonly reported in the literature: 1) rare homozygote vs. common homozygote; 2) heterozygote vs. common homozygote; and 3) heterozygote or rare homozygote vs. common homozygote. We also compared allele frequencies between the case and control infants. Using  $\alpha = 0.05$ , we had adequate power ( $\beta > 0.9$ ) to detect previously described effect sizes for SNP's in the following genes: eNOS, MBL 52, MTHFR 677, MTHFR 1298, and apoE E2 and E4 alleles. We had marginal power ( $\beta = 0.75$ ) to detect previously reported effect sizes for the genes TNF- $\alpha$  and IL-8. Our study had inadequate power ( $\beta = 0.21-0.65$ ) to detect previously described effect sizes in the remaining gene polymorphisms studied. We used a Bonferroni correction to adjust for the multiple case-control comparisons; a P value of 0.001 was considered statistically significant after adjusting for multiple genetic analyses of 15 SNP's. Odds ratios are close approximations of the relative risk, since the outcome of CP is rare in term infants. All analyses were performed using STATA (25) statistical software package.

Study procedures and a waiver of consent were approved by the Institutional Review Boards at Kaiser Permanente Medical Care Program, Utah State University, University of California, San Francisco, and by the California Committee for the Protection of Human Subjects.

## Results

Among 334,333 newborn infants, we identified 377 with spastic or dyskinetic CP. The prevalence of CP among term and near-term infants was 1.1 per 1,000 live births. After applying exclusion criteria, our study included 138 case and 165 control infants. Cerebral palsy was diagnosed by a neurologist in most cases (82%). Spastic hemiparesis (39%) was the most common CP type, followed by spastic quadriplegia (25%). Sixty-one percent of patients had moderate to severe functional impairment (Table 1).

The genotyping yield was 99% for all polymorphisms, with the exception of PAI-1 which was successfully genotyped in only 96% of patients. There was no difference in the rate of successful genotyping between case and control infants. Among the control population, all allele frequencies were in Hardy-Weinberg equilibrium. Control population genotype distributions are listed in Table 2.

First, we compared the rate of CP among children with two copies of the rare allele, to children who were homozygous for the common allele; unlike previous reports whose findings are summarized in Table 3, none of the genetic polymorphisms in our study were associated with increased risk of CP even without adjustment for multiple comparisons (Table 3). The MTHFR 677 polymorphism was associated with a *reduced* risk of CP (OR 0.4, 95% CI 0.2–0.9), but this was also no longer significant after adjusting for multiple comparisons.

We then studied the relationship between genetic polymorphisms and CP by comparing heterozygotes to common homozygotes, as was done in previous studies (Table 3) (6, 8, 10). In these analyses, iNOS -231 (OR 1.9, 95% CI 1.2–3.1) and apoE  $\epsilon$ 4 (OR 1.7, 95% CI 1.01–2.9) were associated with increased risk of CP, but these findings were not significant after adjustment for multiple comparisons. Finally, we compared the rate of CP in children with at least one copy of the rare allele, to children carrying two copies of the common allele. No other associations with CP were found when the genetic variants were analyzed in a dominant genetic comparison (data not shown).

When we compared allele frequencies between case and control infants, we found that the iNOS T allele (25.7% vs. 18.9%,  $P = 0.04$ ) and the apoE  $\epsilon$ 4 allele (19.3% vs. 13.2%,  $P = 0.04$ ) were more common in case than control infants. However, these differences were no longer statistically significant after correction for multiple comparisons.

We stratified our genetic analyses by CP subtype, in order to compare our findings with previous reports (Table 3). No additional information was gleaned from these stratified analyses; i.e., when there was no association between a genetic polymorphism and CP, there was similarly no association seen between that genetic polymorphism and any subset of CP, including diplegic, hemiplegic or quadriplegic CP.

## Discussion

In a study of non-Hispanic white infants born at or near term, we found an increase in the frequency of the apoE  $\epsilon$ 4 and iNOS -231 T alleles in children with CP that was of borderline significance. These associations had small effect sizes, and after adjusting for multiple comparisons in an attempt to avoid false positive findings, we found that these associations were no longer statistically significant.

Genotype-phenotype associations have been observed in many complex diseases; yet most findings have been difficult to replicate (26–28). Cerebral palsy is a complex and heterogeneous condition, and it is not surprising that genetic association studies have

produced inconsistent results. Exploratory studies evaluating a large panel of SNP's often involve numerous statistical analyses stratified by CP subtype, gender, ethnicity and gestational age. Such studies also employ multiple control groups, and perform a variety of genetic comparisons. Thus, in the absence of statistical adjustment for multiple comparisons, exploratory studies testing between 93 and 720 hypotheses (4, 6, 8, 10, 11) would be expected to yield about 5 to 30 genetic associations from chance alone.

Other factors that might contribute to the inconsistent results across studies include small sample size, population heterogeneity, differences in gene-environment interactions and publication bias (3, 26). It is also important to remember that CP is a heterogeneous disorder that results from numerous causal pathways leading to a variety of different types of brain injury, and that lumping all patients with CP into one group further limits our ability to discern meaningful genotype-phenotype associations. Our study is limited by the inclusion of only white infants born at or near term who have spastic or dyskinetic CP. Therefore, our study is not a direct replication of all previous reports, since several past studies have included preterm and non-white infants. Furthermore, we did not perform haplotype analyses or evaluate the presence of viral infections that might modify the relationship between genetic variants and CP (9, 29).

The weak statistical associations identified in our cohort did not persist after adjustment for multiple comparisons. Given the large number of hypotheses that we tested, it was important to perform statistical adjustment to avoid type 1 error. Although we conservatively used the Bonferroni test, any method of adjustment for multiple comparisons would have rendered our findings insignificant, given the P values of 0.04 for the uncorrected genetic associations. However, the weak associations found between the apoE  $\epsilon$ 4 and iNOS -231 T alleles and CP are similar to previous findings in other populations (6, 15, 16), and therefore deserve further discussion.

The relationship between the apoE  $\epsilon$ 4 allele and CP is controversial. Two studies have found a modest increased risk of CP among children who carry at least one  $\epsilon$ 4 allele (15, 16), but a recent meta-analysis suggests that no significant association exists (3). Apolipoprotein E is a lipid transport protein widely expressed in the brain. Carriage of at least one copy of the  $\epsilon$ 4 allele is associated with Alzheimer disease (30) and with ischemic stroke in adults (31, 32). Children with the  $\epsilon$ 4 allele have been shown to exhibit worse neurobehavioral performance and higher birth complication rates (33). We found that children with CP had a higher frequency of carrying an apoE  $\epsilon$ 4 allele, but further large-scale studies will be necessary to determine whether this trend reflects a biologically meaningful relationship.

Similar to previous studies, we found that children with CP were more likely to have a copy of the iNOS -231 T allele, though this finding was not statistically significant after adjustment for multiple comparisons. The iNOS gene was first evaluated in relation to CP because of its role in cardiovascular regulation and ischemic and inflammatory brain injury (2, 6, 34). Over-expression of iNOS in the brain has been reported in newborn periventricular white matter injury (35), as well as in adult stroke (36). In a rat model of newborn brain injury caused by intrauterine infection, iNOS was found to be a key mediator of oligodendrocyte injury (34). Studies comparing iNOS production in patients with and without CP may help us better understand whether genetic variation in the iNOS gene is related to CP risk.

The IL-6 -174 polymorphism has been linked with several adverse perinatal neurologic outcomes including CP (4, 5), periventricular white matter injury (37) and reduced gray matter volume (38). We reported in a single candidate gene study that the IL-6 -174 C allele was associated with a 2.5-fold elevated risk of CP (5), suggesting that an altered fetal

inflammatory response due to genetic variation in inflammatory genes could contribute to a higher risk of CP (4, 8). However, none of the other cytokine gene variants in the current study were significantly associated with CP.

Given the limited sample size, it is possible that our negative results reflect type 2 error due to lack of statistical power, rather than the absence of a true genetic association. Our power analyses suggest that we had adequate power to detect previously described effect sizes for 6 of the polymorphisms studied (s: eNOS, MBL 52, MTHFR 677, MTHFR 1298, and apoE E2 and E4 alleles), and thus our negative findings for these genes, excepting the apoE E4 allele, are relatively robust. Our study had only marginal or poor power to detect previously described associations in all other genetic polymorphisms. Therefore, these other negative findings should be interpreted with caution pending further evaluation in other populations.

Despite the growing number of studies evaluating genetic risk factors for CP, the contribution of genetic factors to CP is likely to be small. The risk of recurrent isolated CP following a first affected child was 0.5% in a US population (39). Among children with CP not due to a brain malformation, genetic syndrome or neurometabolic disease, the recurrence risk is likely to be even smaller. Given the relatively common population occurrence of genetic polymorphisms, and the relatively rare occurrence of CP in term infants, it is unlikely that successful preventative measures will be developed based on genetic risk factors alone, unless we can identify strong gene-environment interactions that confer a significantly increased risk of CP, or we can identify combinations of genetic variants that together signify a particularly high risk of CP. Our data support the evidence that the contribution of genetic factors to CP is likely to be small. Very large-scale studies of genetic, environmental and obstetric factors will be needed before effective preventative strategies can be devised

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## Abbreviations

eNOS	endothelial nitric oxide synthase
EPCR	endothelial protein C receptor
FVL	factor V Leiden
KPMCP	Kaiser Permanente Medical Care Program
iNOS	inducible nitric oxide synthase
MBL	mannose binding lectin
MTHFR	methyltetrahydrofolate reductase
PAI-1	platelet activator inhibitor 1
SNP	single nucleotide polymorphism

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**Table 1**

Characteristics of 138 white infants with cerebral palsy who were born  $\geq$  36 weeks gestation.

	N	%
Evaluated by a neurologist	113	82%
Cerebral palsy type *		
Spastic	125	91%
Choreoathetotic	11	8%
Dystonic or rigid	5	4%
Limb involvement		
Hemiparesis	57	41%
Quadriparesis	38	28%
Paraparesis	34	25%
Monoparesis	2	1%
Unclear	7	5%
Severity of motor impairment		
Mild	53	38%
Moderate	53	38%
Severe	32	23%

\* Note that a child may have more than one type of CP

**Table 2**

Genotype distributions among 165 white control infants without CP

Gene	Polymorphism	Common Homozygote (%)	Heterozygote (%)	Rare Homozygote (%)
TNF-alpha	- 308 G/A	67.9	30.3	1.8
IL-8	- 251 A/T	28.8	49.1	22.1
lymphotoxin	60 C/A	38.3	50.6	11.1
eNOS	- 922 A/G	41.5	47.6	11.0
iNOS	- 231 C/T	65.9	30.5	3.7
EPCR	219 G/A	78.1	20.7	1.2
MBL	54 G/A	70.6	28.2	1.2
MBL	52 A/C	85.9	13.5	0.6
FVL	506 G/A	67.9	30.3	1.8
MTHFR	677 C/T	33.5	52.8	13.7
MTHFR	1298 A/C	50.6	42.0	7.4
Prothrombin	20210 G/A	98.2	1.8	0.0
PAI-1	11053 G/T	34.4	45.0	20.6
ApoE	E3/E4	66.3	20.3	3.1
ApoE	E3/E2	66.3	12.3	0.0

**Table 3**

Summary of previously reported associations between CP and polymorphisms in inflammatory, thrombotic and apolipoprotein E genes, juxtaposed with results of similar analyses performed in the current study. Significant findings *without* adjustment for multiple comparisons highlighted in bold.

Gene (codon)	Previous Studies					Current Study N= 138 White, ≥ 37 weeks			
	CP (N)	Gest (wk)	Demo-graphics	CP Type**	Rare Homozygote vs. Common Homozygote OR (95% CI)	Heterozygote vs. Common Homozygote OR (95% CI)	CP Type	Rare Homozygote vs. Common Homozygote OR (95% CI)	Heterozygote vs. Common Homozygote OR (95% CI)
<b>Inflammatory</b>									
TNF-alpha -308 (8)	65	≥ 37	Whites	QP	0.0 (0.0-1.6)	<b>1.8 (1.04-3.2)</b>	All	1.9 (0.4-8.0)	0.8 (0.5-1.3)
IL-8 -251 (6)	153	< 37	Whites	All	<b>2.4 (1.3-4.4)</b>	<b>2.0 (1.2-3.5)<sup>†</sup></b>	All	1.3 (0.7-2.5)	1.1 (0.7-1.9)
Lymphotoxin 60 (6, 11)	121	All	Whites	DP	0.8 (0.5-1.3) <sup>†</sup>	<b>1.9 (1.2-3.1)</b>	DP	1.7 (0.6-4.9)	1.5 (0.6-3.9)
	356	All	Whites	All	<b>1.5 (1.01-2.18)</b>	1.2 (0.9-1.6) <sup>†</sup>	All	1.3 (0.6-2.7)	0.8 (0.5-1.3)
eNOS -922 (6, 11)	118	All	Whites	HP	<b>1.8 (1.02-3.23)</b>	1.3 (0.9-2.1) <sup>†</sup>	HP	0.9 (0.3-1.4)	0.6 (0.3-1.2)
	110	All	Whites	QP	<b>1.9 (1.01-3.3)</b>	1.5 (0.9-2.4) <sup>†</sup>	QP	1.5 (0.5-4.4)	1.0 (0.5-2.1)
iNOS -231 (6)	96	<32	Whites, Hispanics	All	<b>0.4 (0.1-1.2)<sup>†</sup></b>	<b>1.4 (0.8-2.6)<sup>†</sup></b>	DP	1.6 (0.5-4.8)	0.9 (0.4-2.0)
	96	<32	Whites, Hispanics	All	0.5 (0.1-1.6) <sup>†</sup>	<b>2.2 (1.2-4.0)<sup>†</sup></b>	All	1.4 (0.7-2.9)	0.9 (0.6-1.5)
EPCR 219 (6)	126	All	Whites	DP	<b>0.5 (0.3-0.95)</b>	0.7 (0.5-1.1) <sup>†</sup>	DP	1.7 (0.6-5.0)	0.7 (0.3-1.6)
	180	≥ 37	Whites	All	0.9 (0.5-1.7) <sup>†</sup>	<b>1.6 (1.1-2.2)</b>	All	1.01 (0.3-3.7)	<b>1.9 (1.2-3.1)</b>
MBL 54 (8)	190	≥ 37	Whites	All	0 (0-2.3) <sup>†</sup>	<b>1.6 (1.1-2.3)</b>	All	1.2 (0.2-8.5)	0.9 (0.5-1.6)
	127	All	Whites	DP	0.9 (0.02-6.4) <sup>†</sup>	<b>1.9 (1.2-3.1)</b>	DP	2.4 (0.2-27.1)	0.8 (0.3-2.2)
MBL 52 (8)	49	All	Whites	DP	0.7 (0.1-3.2)	<b>1.6 (1.1-2.4)</b>	All	2.8 (0.5-15.0)	0.7 (0.4-1.3)
	21	≥ 37	Whites	DP	1.2 (0.03-8.1)	<b>2.2 (1.1-4.2)</b>	DP	2.2 (0.2-25.3)	0.6 (0.2-1.5)
<b>Thrombotic</b>									
FVL (506)	1	NA	NA <sup>‡</sup>	HP	NA	NA	All	-	0.8 (0.4-1.8)
MTHFR 677 (10)	58	32-36	Whites	All	<b>2.6 (1.1-5.7)</b>	<b>1.9 (1.01-3.7)</b>	All	<b>0.4 (0.2-0.9)</b>	0.6 (0.4-1.04)
	58	< 32	Whites	DP	<b>2.8 (1.2-6.1)</b>	<b>1.6 (1.02-2.5)</b>	DP	0.5 (0.1-2.0)	0.8 (0.4-1.7)
MTHFR 1298 (10)	20	32-36	Whites	DP	0.5 (0.1-2.3)	<b>0.2 (0.02-0.07)</b>	All	0.6 (0.7-3.8)	0.3 (0.8-2.0)

Gene (codon)	Previous Studies						Current Study N=138 White, ≥ 37 weeks			
	CP (N)	Gest Age (wk)	Demo- graphics	CP Type**	Rare Homozygote vs. Common Homozygote		CP Type	Rare Homozygote vs. Common Homozygote		
					OR (95% CI)	Heterozygote vs. Common Homozygote OR (95% CI)		OR (95% CI)	Heterozygote vs. Common Homozygote OR (95% CI)	
Prothrombin 20210 (10)	20	32-36	Whites	DP	0 (0.0-67.5)	<b>4.3 (0.8-16.6)<sup>‡§</sup></b>	All	-	0.5 (0.1-2.1)	
PAL-1 11053 (6)	150	All	White Girls	All	<b>1.9 (1.1-3.4)</b>	1.6 (0.9-2.6) <sup>‡</sup>	All	1.0 (0.5-2.0)	1.2 (0.7-2.1)	
<u>Apolipoprotein E</u>										
ε4 allele (15, 16)	209	All	White, Hispanic, black	All	2.9 (0.5-30.8) <sup>‡</sup>	<b>3.4 (1.4-8.7)</b>	All	1.6 (0.5-5.6)	<b>1.7 (1.01-2.9)</b>	
	40	All	Brazilian	All	Unknown	<b>5.8 (1.3-34.8)<sup>‡</sup></b>	HP	2.1 (0.5-9.1)	1.9 (0.96-3.8)	
ε2 allele (16-18)	209	All	White, Hispanic, black	All	Unknown	<b>12.0 (1.6-247)</b>	All	-	1.1 (0.6-2.1)	
	106	<32	Whites	All	Unknown	<b>3.5 (1.1-12.7)</b>	HP	-	1.3 (0.6-3.1)	
	243	All	Brazilian	All	Unknown	<b>2.8 (1.01-7.66)</b>	DP	-	1.2 (0.4-3.6)	

\* Note that none of the genetic associations were statistically significant after adjusting for multiple comparisons. Due to space constraints, this table does not include dominant genetic analyses (i.e. rare homozygote or heterozygote, compared to common homozygote). We found no significant associations when data were analyzed with dominant genetic comparisons.

\*\* DP = diplegic, HP = hemiplegic, QP = quadriplegic, All = DP + HP + QP. Note that when a polymorphism was not associated with overall CP, there was similarly no association found between that polymorphism and any subtype of CP.

<sup>‡</sup> These OR's were calculated from the raw data provided in published papers.

<sup>§</sup> NA = not available. An association between FVL and CP has only been reported in case reports and case series, and therefore no risk ratios are available.

<sup>§</sup> The controls used in this calculation were term infants ≥ 37 weeks gestation.