

## Clinical Study

# KIF6 719Arg Carrier Status Association with Homocysteine and C-Reactive Protein in Amnestic Mild Cognitive Impairment and Alzheimer's Disease Patients

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Recent research has demonstrated associations between statin use, KIF6 719Arg carrier status, and cholesterol levels and amnestic mild cognitive impairment (aMCI) and Alzheimer's disease (AD) patients. The association between 719Arg carrier status with homocysteine (tHcy) and c-reactive protein (CRP) levels in aMCI and AD has not been previously investigated. Data from 175 aMCI and AD patients were used for the analysis. 719Arg carriers had significantly lower levels of tHcy than noncarriers ( $P = 0.02$ ). No significant difference in CRP levels between 719Arg carriers and noncarriers was present ( $P = 0.37$ ). Logistic regression yielded no significant effect for 719Arg status on CRP [OR = 1.79 (0.85, 3.83),  $P = 0.13$ ] but did demonstrate a significant effect for tHcy [OR = 0.44 (0.23, 0.83),  $P = 0.01$ ] after adjusting for ApoE  $\epsilon 4$  carrier status, age, gender, and statin use. This study is the first to explore the relationship between KIF6 719Arg carrier status with tHcy and CRP levels. 719Arg carriers were more likely to have normal tHcy levels after adjusting for ApoE  $\epsilon 4$  status, age, gender, and statin use. These results suggest that the KIF6 gene might influence cardiovascular pathways associated with AD.

## 1. Introduction

The KIF6 gene is one of several molecular components involved in the intracellular transport of protein complexes, membrane organelles, and messenger ribonucleic acid along microtubules [1]. There are three polymorphisms of the KIF6 gene which include Arg/Arg, Trp/Arg, and Trp/Trp. Individuals carrying the Arg/Arg or Trp/Arg polymorphisms are classified as 719Arg carriers and have been linked to an increased risk for cardiovascular disease [1–6] relative to 719Arg noncarriers (Trp/Trp). Some of these studies also demonstrated a greater lipid lowering response from statin therapy among 719Arg carriers when compared to noncarriers [1–4]. Others have found no association between 719Arg carrier status and cardiovascular outcomes [7, 8]. A recent study by Sabbagh et al. [9] found that positive 719Arg carrier status combined with statin use was associated with lower total cholesterol (TC) and lower low density lipoprotein (LDL) levels in a sample of amnestic mild cognitive impairment (aMCI) and Alzheimer's disease (AD) patients.

In terms of disease risk, cholesterol levels and statin use have garnered significant attention from aMCI/AD researchers [10–13]; however, homocysteine (tHcy) [14, 15] and c-reactive protein (CRP) [16–18] have also been implicated as risk factors for aMCI and AD. Troen and Rosenberg [19] describe several studies that established elevated tHcy as a risk factor for AD; however, several studies which found no association with tHcy and AD are also cited. Previous research has shown that elevated tHcy may lead to intraneuronal accumulation of A $\beta$ 42 as a result of neurotoxicity which inhibits cellular DNA repair mechanisms [20]. Irizarry et al. [21] found that circulating tHcy correlated moderately with circulating A $\beta$ 42 but concluded that elevated tHcy was not associated with AD or aMCI status.

Elevated CRP has also been established as a risk factor for AD [16–18] and is thought to be associated with inflammatory pathways involved with AD pathogenesis [22]. Bi et al. [23] found that both *in vivo* and *in vitro* CRP cytotoxicity were positively correlated with A $\beta$  formation while Kok et al. [24] demonstrated that allelic variations in the CRP gene

are associated with differing levels senile plaque formation. In contrast, O'Bryant et al. [25] found that AD patients had significantly lower CRP levels relative to controls while Roberts et al. [26] found no association with elevated CRP and amnesic MCI [OR = 1.21; 95% CI (0.81, 1.82)]. Haan et al. [27] found that ApoE  $\epsilon$ 4 carriers had significantly lower CRP levels than noncarriers and that higher CRP levels were associated with a decreased risk of incident all-cause CIND/dementia among ApoE  $\epsilon$ 4 carriers [OR = 0.60; 95% CI (0.20, 0.91)  $P$  = 0.03]. Among cognitively normal older adults, Ravaglia et al. [28] found that ApoE  $\epsilon$ 4 carriers with normal CRP levels had a significantly lower risk of elevated tHcy levels [OR = 0.22; 95% CI (0.08, 0.59)] and were less likely to have elevated CRP levels in the presence of normal tHcy levels [OR = 0.51; 95% CI (0.31, 0.85)] when compared to noncarriers.

Since tHcy and CRP have demonstrated associations with cardiovascular disease [29, 30] and AD [14–18], we sought to investigate whether KIF6 719Arg carrier status is associated with tHcy and CRP in a group of clinically diagnosed AD and aMCI patients. Since KIF6 719Arg carrier status has been previously associated with cardiovascular disease [1–6], investigating its associations with tHcy and CRP in AD is of interest given the proposed cardiovascular pathways for AD pathogenesis [31, 32].

## 2. Method

**2.1. Study Sample.** Data from 175 patients (74 aMCI, 101 AD) between the ages of 53 and 97 who were seen in a neurology clinic in Sun City, AZ, were used for the analysis. All patients were of Caucasian ethnicity. Clinical diagnoses of aMCI and probable or possible AD were made based on medical history, social history, clinical laboratory results, mental status exam, assessment of daily functioning, MRI, and neuropsychological testing. The AD patients met NINCDS-ADRDA [33] criteria for a clinical diagnosis of probable or possible AD. Petersen criteria were used to classify aMCI patients [34]. This study was exempted from review by the Western IRB as it was a study that utilized existing data which was recorded in a way that prevented the identities of the patients from being known.

**2.2. CRP, tHcy, KIF6 Genotype, and ApoE Genotype Processing.** CRP was processed with an automated immunoturbidimetric assay using Roche Modular and tHcy was processed with an enzymatic assay using Roche Modular. KIF6 and ApoE genotyping were processed using real-time PCR (Berkeley Heart Lab, Berkeley, CA).

**2.3. Statistical Analysis.** Chi-square analyses were used to assess differences in frequency for gender, disease status (AD versus aMCI), 719Arg carrier status, and ApoE  $\epsilon$ 4 carrier status. For the Chi-square analyses, a Bonferroni adjusted  $P$ -value of 0.025 was used to correct multiple comparisons. Log transformations were performed on the raw data for tHcy and CRP in order to normalize their distributions. For log-transformed tHcy and CRP values, geometric means with

95% confidence intervals are reported. Group differences between 719Arg carriers and noncarriers for tHcy and CRP were assessed using a two-sample  $t$ -test. Additional two-sample  $t$ -tests were carried out for comparisons of gender, ApoE  $\epsilon$ 4 carrier status, and cholesterol drug (statin) use status on tHcy and CRP.

Logistic regression was used to analyze the associations between tHcy and CRP with 719Arg carrier status in order to provide an estimate of effect size and to provide a more practical interpretation of the associations than the two-sample  $t$ -tests can provide. For these analyses, the sample was dichotomized into elevated and normal groups using recommended clinical guidelines [35] for tHcy and CRP. Individuals with tHcy levels that were  $\geq 14$   $\mu\text{mol/L}$  were classified as elevated while individuals with CRP levels that were  $>3.0$  mg/L were classified as elevated. For the logistic models, elevated/normal status for tHcy and CRP was used as the outcome variable with 719Arg carrier status as the predictor variable. Although dichotomizing continuous variables can result in a loss of statistical power, when the cut-point used has clinical significance this approach is justified [36]. Age, gender, ApoE  $\epsilon$ 4 carrier status, and statin use were used as covariates.

Four different logistic regression models were carried out for both tHcy and CRP using elevated versus normal status as the outcome (8 models total). The first model used only 719Arg carrier status as the predictor variable in order to assess the crude associations with tHcy and CRP. The second model included ApoE  $\epsilon$ 4 carrier status, age, and gender in order to account for their effects. The third model adjusted for statin use in addition to age, gender, and ApoE  $\epsilon$ 4 carrier status. The fourth model used a multiplicative interaction term for 719Arg carrier status and ApoE  $\epsilon$ 4 carrier status (719Arg  $\times$  ApoE  $\epsilon$ 4) as the predictor variable while adjusting for age, gender, and statin use. The fourth model was intended to be an exploratory analysis to further rule out the effect of ApoE  $\epsilon$ 4 carrier status on the association between 719Arg carrier status with tHcy and CRP.

## 3. Results

The study sample was comprised of 82 females and 93 males with an average age of  $77.92 \pm 8.23$  years. Clinical and demographic characteristics of the study sample are displayed in Table 1. For tHcy and CRP, the means and standard deviations of the raw values are reported in addition to the geometric means and their 95% confidence intervals. There was no significant association between 719Arg carrier status, ApoE  $\epsilon$ 4 carrier status, gender, or statin use. There was no significant difference for age or CRP between 719Arg carriers and noncarriers; however, 719Arg carriers had significantly lower tHcy levels. We also analyzed tHcy and CRP by gender, ApoE  $\epsilon$ 4 carrier status, and statin use status (Table 2). The only significant differences noted were for gender and tHcy where males were significantly higher and for ApoE  $\epsilon$ 4 carrier status and CRP where  $\epsilon$ 4 noncarriers were significantly higher than carriers.

TABLE 1: Demographic and clinical characteristics.

	719Arg carriers	719Arg noncarriers	<i>P</i> value
<i>N</i>	106	69	—
Males/females ( <i>n</i> )	54/52	39/30	0.47
ApoE ε4 carrier/noncarrier ( <i>n</i> )	59/47	40/29	0.76
Statin use/no statin use ( <i>n</i> )	59/47	46/23	0.15
Age	77.18 ± 8.58	79.06 ± 7.58	0.13
tHcy (μmol/L) <sup>†</sup>	13.64 ± 4.59	15.12 ± 4.42	—
CRP (mg/L) <sup>†</sup>	4.32 ± 8.49	3.46 ± 8.60	—
tHcy (μmol/L) <sup>‡</sup>	12.94 (12.16, 13.77)*	14.49 (13.46, 15.56)*	0.02
CRP (mg/L) <sup>‡</sup>	1.47 (1.11, 1.96)*	1.21 (0.90, 1.63)*	0.37

Mean ± standard deviation.

<sup>†</sup>Raw scores.

<sup>‡</sup>Log transformed scores.

\*Geometric mean (95% confidence interval).

TABLE 2: Analysis of confounding factors for tHcy and CRP.

	tHcy (μmol/L)	CRP (mg/L)
ApoE ε4 carrier status	Carrier: 13.43 (12.68, 14.22)	Carrier: 1.08 (0.80, 1.44)
	Noncarrier: 13.68 (12.62, 14.83)	Noncarrier: 1.86 (1.40, 2.47)
	<i>P</i> = 0.71	<i>P</i> = 0.01
Gender	Males: 14.32 (13.52, 15.21)	Males: 1.15 (0.84, 1.56)
	Females: 12.68 (11.78, 13.68)	Females: 1.66 (1.25, 2.20)
	<i>P</i> = 0.01	<i>P</i> = 0.08
Statin use status	Statin—yes: 13.15 (12.05, 14.32)	Statin—yes: 1.57 (1.09, 2.28)
	Statin—no: 13.80 (13.06, 14.59)	Statin—no: 1.24 (0.97, 1.59)
	<i>P</i> = 0.32	<i>P</i> = 0.28

Geometric mean (95% confidence interval).

*P*: *P* value.

A post-hoc power analysis for the two-sample *t*-tests found that our sample was large enough to detect a medium effect size ( $d = 0.50$ ) with 90% statistical power [37]. An additional power analysis for the logistic regression analyses demonstrated that our sample achieved 91% power.

Using methods described by Rodriguez et al. [38], we determined whether the frequency of KIF6 and ApoE genotypes were consistent with the Hardy-Weinberg equilibrium. The frequency of KIF6 genotypes did not violate the Hardy-Weinberg equilibrium ( $\chi^2 = 1.44$ ,  $df = 2$ ,  $P = 0.49$ ). The genotype frequency for ApoE ε4 noncarriers did not violate the Hardy-Weinberg equilibrium ( $\chi^2 = 0.30$ ,  $df = 2$ ,  $P = 0.86$ ). However, the genotype frequency for ApoE ε4 carriers did violate the Hardy-Weinberg Equilibrium ( $\chi^2 = 40.09$ ,  $df = 2$ ,  $P < 0.001$ ). The latter is likely due to the fact AD studies tend to have a greater proportion of ApoE ε4 carriers when compared to the genotype's population prevalence [39]. Specifically, the frequency of individuals with the 3/4 genotype ( $n = 80$ ) was substantially greater than the frequencies of the 2/4 ( $n = 4$ ) and 4/4 ( $n = 15$ ) genotypes. The prevalence of the 2/4 genotype (2%) in our study is consistent with population prevalence estimates proposed by Raber et al. [40]; however, the prevalence of the 3/4 (46%) and 4/4 (9%) genotypes in our study are higher than what would be expected in the general population. Given the ε4

genotype's well known association with AD, the violation of the Hardy-Weinberg Equilibrium described above is not surprising. Fisher exact test results found that there was no significant difference in genotype frequency between aMCI and AD patients for KIF6 ( $P = 0.09$ ) and ApoE ( $P = 0.99$ ).

Results of the logistic regression models for tHcy and CRP are displayed in Table 3. 719Arg carrier status showed no significant association with elevated CRP but did demonstrate a significant association with elevated tHcy status even after adjusting for ApoE ε4 carrier status, age, gender, and statin use. The association between 719Arg carrier status and elevated tHcy showed that 719Arg carriers were less likely to have elevated tHcy than noncarriers. The models that tested the KIF6 × ApoE ε4 interaction showed no significant association with elevated tHcy or elevated CRP. We carried out additional logistic regression analyses to assess the associations for ApoE ε4 carrier status with tHcy and CRP as the outcomes. Both analyses yielded nonsignificant results: tHcy [OR = 0.99 (0.54, 1.80),  $P = 0.97$ ]; CRP [OR = 0.58 (0.30, 1.16),  $P = 0.12$ ].

#### 4. Discussion

This study is the first to assess the associations between KIF6 719Arg carrier status with tHcy and CRP in a sample of

TABLE 3: KIF6 719Arg carrier status association with elevated tHcy and CRP.

	tHcy	CRP
Model 1—no adjustment	0.41 (0.22, 0.75) <i>P</i> = 0.004	1.86 (0.90, 3.87) <i>P</i> = 0.10
Model 2—adjusted for ApoE $\epsilon$ 4, age, and gender	0.43 (0.23, 0.82) <i>P</i> = 0.01	1.90 (0.90, 4.01) <i>P</i> = 0.10
Model 3—adjusted for ApoE $\epsilon$ 4, age, gender, and statin use	0.44 (0.23, 0.83) <i>P</i> = 0.01	1.80 (0.85, 3.83) <i>P</i> = 0.13
Model 4—KIF6 $\times$ ApoE $\epsilon$ 4 interaction adjusted for age, gender, and statin use	0.59 (0.30, 1.14) <i>P</i> = 0.12	0.80 (0.38, 1.68) <i>P</i> = 0.55

Odds ratio (95% confidence interval).  
*P* value.

aMCI and AD patients. The results of this study showed that 719Arg carriers had significantly lower tHcy levels relative to noncarriers. Also, 719Arg carriers were also less likely to have elevated tHcy levels relative to noncarriers. Even after adjusting for age, gender, ApoE  $\epsilon$ 4 carrier status, and statin use, the magnitude of the association did not change significantly. The nonsignificant interaction between KIF6 and ApoE on tHcy suggests that the association between KIF6 and tHcy is independent of ApoE. The importance of this finding is highlighted by previous studies demonstrating associations between ApoE and tHcy [28, 41] and suggests that KIF6 might be involved in AD-related cardiovascular pathways that are independent of those associated with ApoE.

Although 719Arg carrier status and CRP were not significantly associated, the direction of the association in this study suggests that 719Arg carriers are more likely to have elevated CRP levels. Even though this association was not statistically significant, it is still interesting to note as ApoE  $\epsilon$ 4 carrier status and statin use were accounted for since both have been associated with decreased CRP [14, 28, 42, 43].

The mechanism by which KIF6 may affect tHcy is unclear as previous studies of KIF6 719Arg carrier status have focused primarily on cholesterol levels, statin use, and incidence of cardiovascular events [1–6]. Based on the results of this study, it is unlikely that statin use has any effect on tHcy levels since there was no significant difference between statin users and nonusers. Further, all of our primary analyses controlled for statin use so it reasonable to conclude that our findings for tHcy and 719Arg carrier status are independent of statin use. However, Maitland-van der Zee et al. [44] found that the presence of certain MTHFR polymorphisms can enhance the beneficial effect of pravastatin in terms of cardiovascular risk reduction and suggest that this association might be due to a statin-induced lowering of tHcy. In a review by Dierkes et al. [45], it was concluded that statin use is not associated with tHcy reduction based on the results of several prospective studies.

An area of interest for future studies would be to assess the role of the MTHFR gene in the relationship between tHcy and KIF6. Since MTHFR is responsible for the metabolism of tHcy, it would be interesting to see if MTHFR polymorphisms interact with KIF6 in terms tHcy levels. Recent evidence

has suggested that the C677T polymorphism of MTHFR is associated with AD independently of ApoE  $\epsilon$ 4 carrier status [46] while Anello et al. [47] reported that the effect of homocysteine as a risk factor for AD was exacerbated when both ApoE  $\epsilon$ 4 and the MTHFR 677T allele were present. Given the results of our study, it would be interesting to see if positive carrier status for KIF6 719Arg mitigates this association since 719Arg carriers in our study had lower overall tHcy levels and a lower risk of having elevated tHcy relative to 719Arg noncarriers. This finding may also be of value to studies in the area of cardiology given the association between elevated homocysteine and cardiovascular disease [48].

Since increased tHcy has been linked to the pathophysiology of AD [49], the role of KIF6 in this pathway may be of importance. Although it is unlikely that KIF6 plays a direct role in AD pathogenesis, it is possible that KIF6 is responsible for certain mediating effects along tHcy-related pathways for AD. The results of this study suggest that carriers of the KIF6 719Arg allele have a preferential tHcy profile that may provide some level of protection along AD-related cardiovascular pathways involving tHcy.

## Conflict of Interests

The authors have no conflict of interests to disclose.

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