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KIF6 719Arg Allele is Associated with Statin Effects on Cholesterol Levels in Amnesic Mild Cognitive Impairment and Alzheimer's Disease Patients

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Abstract

KIF6 719Arg allele carriers are thought to have a greater lipid lowering response from statin therapy than non-carriers. Given the continued interest in the relationship between cholesterol, statin use, amnesic mild cognitive impairment (aMCI), and Alzheimer's disease (AD) investigating the role of KIF6 719Arg carrier status in these relationships may be of importance. Data from 86 patients (36 aMCI, 50 AD) with an average age of 76.87±8.22 years were used for this study. Total cholesterol (TC), low density lipoprotein (LDL), high density lipoprotein (HDL), and triglycerides were the outcome variables. 719Arg carriers taking statins had significantly lower TC ($p < .001$) and LDL ($p < .001$) levels than 719Arg carriers not taking statins. In addition, 719Arg carriers not taking statins had significantly higher TC ($p = .004$) and LDL ($p < .001$) than 719Arg non-carriers taking statins. Additional analyses indicated that ApoE ε4 carrier status and statin use interaction is also associated with lower TC ($p = .04$), but not LDL ($p = .06$). The interaction between 719Arg and ApoE ε4 carrier status on TC and LDL was not significant. This study is the first to demonstrate an association between lower cholesterol levels and statin use among KIF6 719Arg allele carriers with aMCI and AD. Accounting for 719Arg carrier status may be important in future studies investigating the link between cholesterol and AD and also for AD and aMCI clinical trials using statins as a treatment.

Keywords

mild cognitive impairment; Alzheimer's disease; cholesterol; KIF6; ApoE4

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 coronary events [1–6] when compared to 719Arg non-carriers (Trp/Trp). In addition, 719Arg carriers are also thought have a greater lipid lowering response from statin therapy than non-carriers [1–6]. Others have found no association between 719Arg carrier status and cardiovascular

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outcomes [7,8]. The findings of 719Arg carrier status and improved statin response could be of great interest to the area of Alzheimer's disease (AD) research as several studies have shown associations between increased cholesterol levels and incident AD [9–12].

A study by Sabbagh et al [13] found that a sample of AD patients had higher total cholesterol (TC), higher low density lipoprotein (LDL), and higher triglyceride (TG) levels when compared to a group of non-demented individuals. Jarvik et al [14] found that higher TC levels were associated with earlier age of AD onset in carriers of the ApoE ϵ 4 allele. In contrast, Presecki et al [15] found that AD patients had significantly lower LDL levels when compared to non-demented controls. A review by Solfrizzi et al [16] cited several conflicting studies regarding the relationship between TC and AD in which some showed a protective effect while others demonstrated either a risk increase for higher levels of TC or no significant relationship between TC and AD. Sabbagh and Sparks [17] state that statins may have neuroprotective properties and they also cite neuropathological studies which showed that individuals taking statins have reduced plaque and tangle counts. Several clinical trials using statins to treat Alzheimer's disease have been conducted, however, the results of these trials have been mixed with one showing a significant positive effect [18] and some showing no effect [19,20]. A recent systematic review concluded that statin use is not an effective treatment for AD [21]. Sabbagh and Sparks propose that participant selection based on cholesterol levels might account for several of these trials' failures [17] as one trial that enrolled AD patients with elevated cholesterol levels did show a significant effect [22]. Other studies have demonstrated that cognitively normal individuals taking statins may have a reduced risk for developing AD [23–26].

Given the findings of previous studies showing that 719Arg carriers have strong reduction in cholesterol in response to statin therapy, investigating the role of 719Arg carrier status in AD may help select subjects that might more robustly respond to statins for treatment and prevention studies [27,28]. The aim of this study is to characterize 719Arg carrier status and statin use in a clinical sample of amnesic mild cognitive impairment (aMCI) and AD patients as measured by a comprehensive lipid panel.

Materials and Method

Study Sample

Data from 86 patients (36 aMCI, 50 AD) between the ages of 53 and 93 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 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 [29] criteria for a clinical diagnosis of probable and possible AD. Petersen criteria were used to classify aMCI patients [30].

Individuals were grouped into one of four categories based on 719Arg carrier status and current statin use. The 719Arg Carrier / Statin – Yes group refers to 719Arg carriers taking statins, the 719Arg Carrier / Statin – No group refers to 719Arg carriers not taking statins, the 719Arg Non-Carrier / Statin – Yes group refers to 719Arg non-carriers taking statins, and the 719Arg Non-Carrier / Statin – No group refers to 719Arg non-carriers not taking statins.

Lipid Panel and KIF6 Genotype Processing

The lipid panel (total cholesterol [TC], low density lipoprotein [LDL], high density lipoprotein [HDL], and triglycerides) was processed using an enzymatic-colorimetric assay

using Roche Modular [31]. KIF6 genotyping was processed using real-time PCR (Berkeley Heart Lab, Berkeley, CA).

Statistical Analysis

Chi-square analysis was used to determine if significant differences in frequencies between 719Arg carrier status were present between statin users and non-users and also between 719Arg carrier status and gender existed. Analysis of covariance (ANCOVA) was used to determine group differences on the individual lipid panel measures between 719Arg carriers and non-carriers who were taking or not taking statins. Age was entered as covariate in order to account for its effect. Bonferroni adjustment was used to correct for multiple group comparisons. Linear regression models were used to determine the individual and interaction effects of 719Arg carrier status, ApoE ε4 carrier status, and statin use status on TC and LDL levels. Findings $p < 0.05$ were considered to be statistically significant. Statistical analyses were carried out using SYSTAT 13 (SYSTAT Software, Inc., Chicago, IL).

Results

Of the 86 individuals in the sample, 46 were male and 40 were female. The average age of the sample was 76.87 ± 8.22 years. The average age for males was 78.04 ± 8.40 years and 75.53 ± 7.89 for females. This difference was not statistically significant [$t = -1.43$ ($df = 84$) $p = 0.16$]. 719Arg non-carriers were significantly older (78.94 ± 7.67) than 719Arg carriers (75.45 ± 8.35) [$t = 1.97$ ($df = 84$) $p = 0.05$]. There was no significant difference in age between those taking and not taking statins.

Among the study sample, approximately 66% ($n = 57$) were on statin therapy. 58% ($n = 50$) of the sample were 719Arg carriers. The breakdown of KIF6 polymorphism frequency among the study sample was Trp/Trp = 36, Trp/Arg = 40, and Arg/Arg = 10. There was no significant association between 719Arg carrier status and statin use ($\chi^2 = 1.69$, ($df = 1$) $p = 0.19$). There was no significant association between 719Arg carrier status and gender ($\chi^2 = 0.32$, ($df = 1$) $p = 0.57$).

Table 1a displays the lipid panel results for 719Arg carriers who were and were not taking statins. The 719Arg Carrier / Statin – Yes group had significantly lower TC and LDL than the 719Arg Carrier / Statin – No group. No significant differences were found for HDL and triglycerides. Large effect sizes were also noted for TC and LDL. Table 1b displays the lipid panel results for 719Arg non-carriers who were and were not taking statins. No significant group differences were present among the lipid panel measures for this analysis.

No statistically significant differences were found between the 719Arg Carrier / Statin – Yes group and the 719Arg Non-Carrier / Statin – Yes group for TC ($p = 0.99$), LDL ($p = 0.99$), HDL ($p = 0.99$), or triglycerides ($p = 0.99$). Analyses for 719Arg carriers and non-carriers who were not taking statins also failed to yield statistically significant group differences for TC ($p = 0.13$), LDL ($p = 0.20$), HDL ($p = 0.99$), and triglycerides ($p = 0.42$). Despite the lack of statistical significance for TC and LDL, large effect sizes were noted for these two variables between the groups (TC, $d = 0.91$; LDL, $d = 0.91$).

Linear regression analyses were carried out to investigate the separate and interactive effects of 719Arg carrier status, ApoE ε4 carrier status and statin use status on TC and LDL levels. The linear regression results for TC and LDL are displayed in Tables 2a and 2b, respectively. For TC, 719Arg carrier status demonstrated a statistically significant effect ($p = 0.02$) as did the interaction effect of 719Arg carrier status and statin use ($p = 0.005$). The ApoE ε4 and statin use interaction was also statistically significant ($p = 0.04$). Statin use (p

= 0.14), ApoE ϵ 4 carrier status ($p = 0.53$), and the interaction between ApoE ϵ 4 carrier status and 719Arg carrier status ($p = 0.39$) were not statistically significant.

For LDL, only 719Arg carrier status ($p = 0.02$) and the interaction effect of 719Arg and statin use ($p = 0.01$) demonstrated statistically significant effects. The interaction between ApoE ϵ 4 carrier status and statin use approached statistical significance ($p = 0.06$), while ApoE ϵ 4 carrier status ($p = 0.72$), statin use status ($p = 0.08$), and the interaction between ApoE ϵ 4 carrier status and 719Arg carrier status ($p = 0.28$) were not statistically significant.

Discussion

This study is the first to demonstrate differences in cholesterol levels among KIF6 719Arg carriers on statin therapy when compared with 719Arg carriers not taking statins in a sample of MCI and AD patients. These findings are consistent with other studies that have found 719Arg carriers to have significantly lower TC and LDL levels with statin therapy [1–6]. This study also found that 719Arg carriers not taking statins had the highest TC and LDL levels among the study sample. The lack of statistical significance between 719Arg carriers and non-carriers not taking statins may be due to the relatively small number of cases in the 719Arg Carrier / Statin – No group. In particular, the large effect sizes noted for TC and LDL suggests that there is some meaningful difference between these two groups. The proportion of individuals on statin therapy in the study (66%) is relatively high and reflects high prevalence of hypercholesterolemia that occurs in AD.

The relationship between 719Arg carrier status and cholesterol levels is underscored by the significant interaction effects observed in this study. For both TC and LDL, 719Arg carrier status and statin use appear to have a synergistic effect in lowering cholesterol levels. These results also show that ApoE ϵ 4 carrier status might also have a significant role in the relationship between statin use and cholesterol levels. This study found a significant interaction between ApoE ϵ 4 carrier status and statin use for TC, but not for LDL. The reason for this is unclear, but it is possible that ApoE ϵ 4 carrier status might also mediate a cholesterol lowering response with statin therapy. However, the mechanisms of cholesterol processing for ApoE ϵ 4 and 719Arg appear to work separately from each other as their interaction effect on TC and LDL was not significant. These findings are highly relevant given that ApoE ϵ 4 carrier status has been implicated as a risk factor for both AD [32,33] and cardiovascular disease [34,35].

Since this study did not include a control group of cognitively normal individuals, this study was unable to address how 719Arg carrier status might influence the risk of aMCI/AD. This is one major weakness of the study which is due to its design. Additionally, the study could not evaluate the effects of 719Arg carrier status and lipid metabolism on clinical status (Normal, aMCI, AD) due to the lack of a control group. However, future studies should address these issues since previous research has suggested that midlife TC level is a significant predictor of incident AD [9]. Another weakness of the study is homogeneity of the study sample. Since all individuals in the sample were Caucasian, differences due to ethnicity that might occur in the associations between 719Arg carrier status and cholesterol levels are not captured in this study.

The extent to which statins have a therapeutic effect on cognition in aMCI and AD is unclear. Sparks et al [36] report that higher levels of TC and LDL are detrimental to cognition while increased HDL is associated with better cognitive performance. Others have also reported improved cognitive performance with increasing HDL levels [37, 38]. In contrast, others have demonstrated improved cognition with increased TC and LDL [39]. The relationship between cholesterol and AD pathophysiology is complex, but is thought to

involve processes that include beta and gamma secretase cleavage of APP, overproduction of beta amyloid triggered by cholesterol, and ApoE interactions [40].

The findings of this study highlight the need for 719Arg carrier status to be accounted for in therapeutic and prevention trials for aMCI and AD. Given the conflicting findings of clinical trials using statins to treat AD [18–22], it is possible that the proportion of 719Arg allele carriers in the respective study samples may have contributed to whether or not a significant cognitive treatment effect was observed. Sabbagh et al [41] propose that genotyping and baseline cholesterol levels may be important methodological factors in aMCI/AD statin clinical trials which underscores the importance of accounting for a gene associated with lower levels of cholesterol with statin therapy.

Although the relationship between cholesterol levels, statin use, and AD is still under investigation, the results of this study show that accounting for KIF6 719Arg carrier status should be incorporated into the designs of future studies in aMCI and AD given the established associations between cholesterol and cognition. Determining the extent to which changes in cognition are related to changes in cholesterol and whether this relationship is mediated by 719Arg carrier status could help elucidate the effect of statins on aMCI/AD disease progression. In light of the conflicting evidence among clinical trials using statins in AD, accounting for 719Arg carrier status may have significant methodological importance for future therapeutic aMCI and AD trials using statin therapy.

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Table 1a

Demographic Characteristics and Lipid Panel Results for 719Arg Carriers by Statin Therapy Status

	<i>719Arg Carrier/Statin – Yes</i>	<i>719Arg Carrier/Statin – No</i>	<i>p-value</i>	<i>d</i>
Male (n)	20	6	-----	-----
Female (n)	11	14	-----	-----
ApoE e4 Carrier / Non-Carrier (n)	21 / 10	13 / 7	-----	-----
Age	73.96 (9.93)	76.57 (6.61)	0.99	0.31
Total Cholesterol	171.26 (33.44)	224.65 (39.37)	<.001	1.46
LDL	89.26 (24.55)	131.55 (31.31)	<.001	1.50
HDL	55.39 (16.57)	59.90 (18.69)	0.99	0.26
Triglycerides	132.87 (67.20)	165.95 (86.81)	0.92	0.43

Mean (sd); ns – non-significant; *d* – Cohen's *d*

Table 1b

Demographic Characteristics and Lipid Panel Results for 719Arg Non-Carriers by Statin Therapy Status.

	<i>719Arg Non-Carrier/Statin – Yes</i>	<i>719Arg Non-Carrier/Statin – No</i>	<i>p-value</i>	<i>d</i>
Male (n)	16	4	-----	-----
Female (n)	10	5	-----	-----
ApoE e4 Carrier / Non-Carrier (n)	13 / 13	6 / 3	-----	-----
Age	80.04 (6.35)	77.50 (6.50)	0.99	0.40
Total Cholesterol	183.58 (39.56)	189.67 (37.72)	0.99	0.52
LDL	96.08 (32.36)	106.78 (22.58)	0.99	0.74
HDL	57.69 (19.39)	61.56 (20.22)	0.99	0.18
Triglycerides	159.39 (96.05)	107.11 (45.05)	0.57	0.70

Mean (sd); ns – non-significant; *d* – Cohen's d

Table 2a

Separate and Combined Effects of KIF6 719Arg, ApoE ε4, and Statin Use on Total Cholesterol

<i>Variable</i>	<i>t-value</i>	<i>p-value</i>
719Arg	2.41	.02
ApoE ε4	−0.63	.53
Statin Use Status	−1.48	.14
719Arg × Statin Use Status	−2.90	.005
ApoE ε4 × Statin Use Status	2.11	.04
719Arg × ApoE ε4	−0.86	.39

Overall Linear Regression Model: $F = 5.58$, $df = (6, 79)$, $p < .001$, adjusted $R^2 = .26$

Table 2b

Separate and Combined Effects of KIF6 719Arg, ApoE ε4, and Statin Use on LDL

<i>Variable</i>	<i>t-value</i>	<i>p-value</i>
719Arg	2.40	.02
ApoE ε4	−0.36	.72
Statin Use Status	−1.76	.08
719Arg × Statin Use Status	−2.56	.01
ApoE ε4 × Statin Use Status	1.90	.06
719Arg × ApoE ε4	−1.10	.28

Overall Linear Regression Model: $F = 6.01$, $df = (6, 79)$, $p < .001$, adjusted $R^2 = .26$