Investigation of KIF6 Trp719Arg gene polymorphism in a case-control study of coronary artery disease and non-fatal myocardial infarction in the Eastern Province of Saudi Arabia

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BACKGROUND: Kinesin-like protein 6 (KIF6), a member of the kinesin superfamily, is involved in intracellular transport. A few prospective studies have shown the KIF6 variant Trp719Arg (rs20455) to be associated with coronary artery disease (CAD) in Caucasian populations. However, recent genome-wide association studies on CAD have not proven these associations.

OBJECTIVES: Since the role of KIF6 719Arg allele in other ethnic populations is largely unknown, we sought to determine whether the KIF6 719Arg allele is associated with CAD in an ethnic population of Saudi Arabia.

DESIGN: Case-control study.

SETTING: CAD patients and control subjects from King Fahd Hospital of the University, Al-Khobar, Saudi Arabia.

PATIENTS AND METHODS: The study population included angiographically defined CAD patients (n=1002) and controls (n=984) with a normal electrocardiogram.

MAIN OUTCOME MEASURE(S): Association of KIF6 Trp719Arg mutation with CAD.

RESULTS: The KIF6 Trp719Arg polymorphism was not associated with CAD (OR 0.976, 95% CI 0.861-1.105; P=.704). In addition, KIF6 Trp719Arg polymorphism showed a lack of association even in stratified myocardial infarction patients (n=802) (OR 1.006, 95% CI 0.881-1.148; P=.929) in comparison to controls.

CONCLUSIONS: The absence of Trp719Arg polymorphism association with CAD and CAD in stratified myocardial infarction cases indicates that the polymorphism is not associated with an increased risk among CAD patients from the Eastern Province of Saudi Arabia. Further studies in different provinces are required to unravel biological mechanisms underlying CAD in patients from Saudi Arabia.

LIMITATIONS: Unavailability of data on statin usage among the patient population.

Coronary artery disease (CAD), also known as coronary heart or ischemic heart disease, is characterized by an inadequate supply of oxygenated blood to the myocardium due to narrowing of the coronary artery by fatty plaques. The disease has a multifactorial etiology caused by genetic and environmental factors. The known risk factors for CAD include age, sex, family history, smoking status, high blood pressure, high blood cholesterol, stress and reduced physical activity. The risk of CAD is influenced by genetic variations in pathways involving lipoprotein and glucose metabolism, inflammation,
oxidation, adhesion, homeostasis and gene regulation. A number of genetic loci, candidate genes and single nucleotide polymorphisms (SNPs) are associated with an increased susceptibility to CAD with no consistent variant or gene identified.

The kinesin-like protein 6 (NM_145027) gene encodes kinesin, which is a motor protein involved in the intracellular transport of membrane organelles, protein complexes, and mRNAs along the microtubule. This protein has a non-conserved tail domain with a coiled-coil structure that binds to its cargo and facilitates protein-protein interactions and transport. The 3972bp KIF6 gene (locus – 6p21.2) spans over 23 exons and the Trp719Arg polymorphism is located on exon 19 in the tail domain. Consequently, this non-conservative amino acid change that replaces a non-polar residue (Trp) with a basic residue (Arg), affects its cargo-binding capacity. Trp and Arg are considered as wild type and mutant, respectively. Several kinesins have been implicated in the pathogenesis of chronic diseases, such as neurodegenerative disorders, type 2 diabetes, hypertension, Alzheimer’s disease and for adverse cardiovascular outcomes after myocardial infarction.

Multiple large prospective cohort studies from Scotland (WOSCOPS) and the United States (CARE and ARIC) have shown that carriers of the KIF6 719Arg allele have an increased risk for CAD among populations of European ancestry. The first results from a prospective study were obtained from observational studies of the Atherosclerosis Risk in Communities (ARIC) study followed by the Cholesterol and Recurrent Events (CARE) trial, the West of Scotland Coronary Prevention Study (WOSCOPS), the Cardiovascular Health Study (CHS), the Women’s Health Study (WHS) and the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER). Carriers of the 719Arg allele showed a 20% increased risk for CAD when compared with non-carriers in a meta-analysis including seven prospective studies. This elevated risk was independent of traditional risk factors. However, genome-wide association studies on CAD did not prove these associations. Only sparse data are available on whether the KIF6 719Arg allele is associated with CAD in other ethnic populations. To the best of our knowledge, the present study is the first to report the KIF6 719Arg frequency from Saudi Arabia. The main motive for the study is the high incidence of CAD cases among the population of Saudi Arabia. The primary aim is to understand whether the KIF6 719Arg allele is associated with CAD and non-fatal MI in the population of the Eastern Province of Saudi Arabia.

**PATIENTS AND METHODS**

This case-control study from the Eastern Province of Saudi Arabia included 1002 angiographically defined CAD patients, including individuals who had survived up to six MI events. The blood samples were collected in EDTA-coated vacutainers from patients attending the cardiac clinic at King Fahd Hospital of the University during the period 2012–2014. The control group consisted of subjects recruited from the blood bank at King Fahd Hospital of the University, Al-Khobar. In the 984 control subjects, absence of CAD was confirmed by electrocardiogram and a lack of a family history of CAD. The family history and the co-existing conditions were recorded on a data form predesigned for the study and clinical examination records were collected from the hospital database. Lipid profile was determined for all subjects using a Flex reagent cartridge on Siemens Dimension RxL chemistry system (http://goo.gl/xpBQTB). The criteria for diabetes mellitus was a glucose concentration of >126 mg/dL during fasting and for hypertension it was ≥140 mm Hg for systolic and/or ≥90 mm Hg for diastolic blood pressure. All patients and controls resided in the Eastern Province of Saudi Arabia. Study and consent documents were approved by the ethical committee of the University of Dammam. All the participants in the research study gave written informed consent.

**Genotyping**

DNA was isolated from EDTA anti-coagulated blood samples using QIAamp DNA isolation kit (Qiagen, UK, https://goo.gl/c-RblO0) as per the manufacturer’s instructions. DNA concentration and purity was measured using Nanodrop 2000 UV-Vis spectrophotometer (Nanodrop, USA, http://goo.gl/36vwQh). The KIF6 Trp719Arg polymorphism was genotyped using an allele specific Taqman genotyping assay by real-time PCR (ABI 7500, USA, https://goo.gl/QFgPJz). The ABI TaqMan assay reagents (Cat no. 4353179, Thermo Fisher Scientific, USA, http://goo.gl/idVRvT) were used for the detection of a mutation which used dyes FAM/VIC with excitation at 470nm, 530nm and emission at 510nm, 557nm corresponding to green and yellow channels, respectively. The thermo-cycling conditions were 1 cycle of 10 min at 95°C; 40 cycles of 15 sec at 92°C, 1 min at 60°C.

**Statistical analysis**

Deviations from Hardy-Weinberg equilibrium were assessed using the Michael H. Court programme (Michael H. (2012) Court’s (2005–2008) online calculator. Tuft University). The baseline characteristics of cases and controls were compared using t-test.
test for continuous variables and Fisher’s exact test for discrete variables. Allele frequencies were estimated by direct counting of the test allele divided by the total number of alleles. Genotypic and allele association with the disease were assessed by the chi-square test. To assess the risk for CAD, odds ratios was determined. All statistical analyses were performed using SPSS software (version 19, https://goo.gl/G0S4LT) and considered significant if the \( P \) value was <.05. Based on the observed genotype frequencies in the present study, assuming genetic effect between 1.5 and 1.2 our design can reach >98% power when the risk is 1.5 and 56% power when the risk is 1.2.

RESULTS

Of the 1002 CAD patients recruited for the study, 778 had experienced at least one MI, 24 had experienced between three to six MIs and 200 had no history of MI (Table 1). Statistically significant differences were seen in gender (\( P <.0001 \)), prevalence of diabetes (\( P <.0001 \)), and prevalence of hypertension (\( P <.0001 \)) in cases versus controls (n = 984). The mean age of the patient group was 59.5 (12.6) years and the mean age of the control group was 55 (11.1) years. Male predominance was seen in both the patient (52.8%) and control (79.6%) groups. Among the patient group, 55.2% had hypertension (HTN) and 51.4% had diabetes (DM). In the patient population, 80% had experienced between one to six MI events.

The genotype and allele frequency of the \( KIF6 \) Trp719Arg (rs20455) SNP are shown in Table 2. None of the SNPs deviated from the Hardy-Weinberg equilibrium. The \( KIF6 \) Trp719Arg (rs20455) SNP showed no association with CAD (OR 0.976 95% CI 0.86-1.11; \( P =.704 \)). We stratified the CAD patients into two groups, the MI group (OR 1.0; 95% CI 0.88–1.14; \( P =.929 \)) and the non-MI group (OR 0.864; 95% CI 0.69–1.07; \( P =.187 \)). However, no association between the tested SNP and an increased risk of CAD was found (Tables 3 and 4). Further analysis based on gender also revealed a lack of association between \( KIF6 \) 719Arg and an increased risk of CAD (Tables 5 and 6).

DISCUSSION

Limited data are available on whether the \( KIF6 \) Trp719Arg allele is associated with CAD in ethnic populations other than the predominantly studied populations of European ancestry. To the best of our knowledge, this is the first study that reports the frequency of this variant in the Saudi Arabian population. The \( KIF6 \) Trp719Arg variant (rs20455) has been associated with CAD in only a few prospective studies.\(^{10-13}\) The minor allele frequency (MAF) of rs20455 ranged from 0.10 (YRI, Yoruba in Ibadan, Nigeria) to 0.48 (JPT, Japanese in Tokyo, Japan) as per the HapMap database. In the present study, the ob-

**Table 1.** General characteristics of cases and controls.

| Characteristics          | Patient (n=1002) | Control (n=984) |
|--------------------------|------------------|----------------|
| Gender (M:F)             | 529 (52.8):473 (47.2)\(^a\) | 783 (79.6): 201 (20.4) |
| Age (years)              | 59.5 (12.6)      | 55 (11.1)     |
| Hypertension, n (%)      | 553(55.2)\(^a\)  | 25 (2.54)     |
| Diabetes, n (%)          | 515 (51.4)\(^a\) | 22 (2.23)     |
| Total cholesterol (mg/dL)| 172.4 (50.1)     | 197.2 (34.1)  |
| HDL cholesterol (mg/dL)  | 38.1 (15)        | 41.2 (11.6)   |
| LDL cholesterol (mg/dL)  | 104 (43.9)       | 128 (28.5)    |

\(^aP<.0001\) (Fisher exact test), HDL: high density lipoprotein; LDL: low density lipoprotein. Data are mean (standard deviation).

**Table 2.** Genotype and allele frequency among patient and control populations.

| rs20455  | Cases, n (%) | Control, n (%) | OR  | 95% CI     | \( P \) value |
|----------|--------------|----------------|-----|------------|---------------|
| Genotype |              |                |     |            |               |
| TT       | 277 (27.6)   | 286 (29)       |     | Reference  |               |
| TC       | 513 (51.2)   | 464 (47.2)     | 1.1415 | 0.927-1.404 | .211          |
| CC       | 212 (21.2)   | 234 (23.8)     | 0.9354 | 0.729-1.199 | .598          |
| Allelic model |       |                |     |            |               |
| T        | 1067 (53.2)  | 1036 (52.6)    |     | Reference  |               |
| C        | 937 (46.8)   | 932 (47.4)     | 0.9762 | 0.861-1.105 | .704          |
| Dominant model |    |                |     |            |               |
| TT vs TC+CC | 725 (72.4) | 698 (71)       | 1.0724 | 0.882-1.303 | .482          |
| Recessive model |     |                |     |            |               |
| CC vs TT+TT | 790 (78.9) | 750 (76.2)     | 1.1626 | 0.945-1.435 | .161          |
| HWE P value | --       | 0.37           | 0.088 | --         | --            |

OR: Odds ratio; 95% CI: 95% confidence interval, HWE: Hardy-Weinberg Equilibrium.
served MAF was 0.47 which was consistent with 1000 genome (0.460) and HapMap. The ARIC study among African Americans showed that the KIF6 variant increased the incidence risk for CAD by 1.23-fold.10 In addition, an association between MI and the KIF6 variant was seen in the African American population12 and in the Han Chinese population.19 Thus, these results suggested that the KIF6 719Arg allele may be associated with CAD in ethnic populations other than those of European ancestry.

In contrast, other literature has reported a lack of association for the same risk allele among various populations. Assimes et al16 reported a non-association of the KIF6 polymorphism with CAD in 19 studies with a total of 17,000 cases and 39,369 controls in Europeans, South Asians, African Americans, East

| Table 3. Association between KIF6 Trp719 Arg genotype and MI cohort. |
|-------------------|-----------------|----------|------|-------|--|---|
| rs20455            | MI cases, n (%) | Control, n (%) | OR  | 95% CI  | P value |
| Genotype           |                 |            |      |        |   |   |
| TT                | 217 (27.1)  | 286 (29) | 1.158 | 0.929-1.445 | .19 |
| TC                | 408 (50.9)  | 464 (47.2) | 1.089 | 0.881-1.348 | .29 |
| CC                | 177 (22)    | 234 (23.8) | 0.996 | 0.766-1.297 | .981 |
| Allelic model     |                 |            |      |        |   |   |
| T                 | 842 (52.5)  | 1036 (52.6) | 1.064 | 0.878-1.286 | .72 |
| C                 | 762 (47.5)  | 932 (47.4) | 1.00 | 0.881-1.148 | .929 |
| Dominant model    |                 |            |      |        |   |   |
| TC+CC             | 585 (72.9)  | 698 (71)  | 1.044 | 0.897-1.359 | .348 |
| Recessive model   |                 |            |      |        |   |   |
| TC+TT             | 625 (77.9)  | 750 (76.2) | 1.011 | 0.882-1.375 | .393 |

OR: Odds ratio; 95% CI: 95% confidence interval.

| Table 4. Association between KIF6 Trp719 Arg genotype and non-MI cohort. |
|-------------------|-----------------|----------|------|-------|--|---|
| rs20455            | Non-MI cases, n (%) | Control, n (%) | OR  | 95% CI  | P value |
| Genotype           |                 |            |      |        |   |   |
| TT                | 60 (30)        | 286 (29) | 1.078 | 0.760-1.530 | .671 |
| TC                | 105 (52.5)    | 464 (47.2) | 0.713 | 0.454-1.119 | .141 |
| CC                | 35 (17.5)     | 234 (23.8) | 1.00 | 0.665-1.530 | .187 |
| Allelic model     |                 |            |      |        |   |   |
| T                 | 225 (56.3)    | 1036 (52.6) | 0.956 | 0.685-1.332 | .791 |
| C                 | 175 (43.7)    | 932 (47.4) | 1.00 | 0.696-1.073 | .187 |
| Dominant model    |                 |            |      |        |   |   |
| TC+CC             | 140 (70)      | 698 (71)  | 0.956 | 0.685-1.332 | .791 |
| Recessive model   |                 |            |      |        |   |   |
| TC+TT             | 165 (82.5)    | 750 (76.2) | 1.470 | 0.992-2.179 | .054 |

OR: Odds ratio; 95% CI: 95% confidence interval.

| Table 5. Association between KIF6 Trp719 Arg genotype and CAD in male cohort. |
|-------------------|-----------------|----------|------|-------|--|---|
| rs20455            | Cases, n (%) | Control, n (%) | OR  | 95% CI  | P value |
| Genotype           |                 |            |      |        |   |   |
| TT                | 137 (25.9)    | 229 (29.2) | 1.292 | 0.995-1.678 | .054 |
| TC                | 290 (54.8)    | 375 (47.9) | 0.952 | 0.690-1.314 | .767 |
| CC                | 102 (19.3)    | 179 (22.8) | 1.00 | 0.651-1.336 | .897 |
| Allelic model     |                 |            |      |        |   |   |
| T                 | 564 (53.3)    | 833 (53.2) | 1.00 | 0.851-1.163 | .953 |
| C                 | 494 (46.7)    | 733 (46.8) | 0.995 | 0.851-1.163 | .953 |
| Dominant model    |                 |            |      |        |   |   |
| TC+CC             | 392 (74.1)    | 554 (70.7) | 1.182 | 0.922-1.515 | .184 |
| Recessive model   |                 |            |      |        |   |   |
| TC+TT             | 427 (80.7)    | 604 (77.1) | 1.24 | 0.944-1.629 | .121 |

OR: Odds ratio; 95% CI: 95% confidence interval.
Table 6. Association between KIF6 Trp719Arg genotype and CAD in female cohort

| rs20455 | Cases, n (%) | Control, n (%) | OR     | 95% CI | P value |
|---------|-------------|----------------|--------|--------|---------|
| Genotype |             |                |        |        |         |
| TT      | 140 (29.6)  | 57 (28.3)      | Reference |        |         |
| TC      | 223 (47.1)  | 89 (44.3)      | 1.02    | 0.687-1.512 | .921   |
| CC      | 110 (23.3)  | 55 (27.4)      | 0.814   | 0.520-1.272 | .367   |
| Allelic model | | | | | |
| T       | 503 (53.2)  | 203 (50)       | Reference |        |         |
| C       | 443 (46.8)  | 199 (50)       | 0.898   | 0.711-1.134 | .368   |
| Dominant model | | | | | |
| TC+CC   | 333 (70.4)  | 144 (71.6)     | 0.941   | 0.653-1.355 | .746   |
| Recessive model | | | | | |
| TC+TT   | 363 (76.7)  | 146 (72.6)     | 1.243   | 0.853-1.811 | .257   |

OR: Odds ratio; 95% CI: 95% confidence interval.

Table 7. KIF6 studies comparison in different populations.

| Population         | OR/HR | P value | Reference |
|--------------------|-------|---------|-----------|
| Association studies|       |         |           |
| African American   | 1.22  | .033    | Bare et al10 |
| Caucasian          | 1.5   | .03     | Iakoubova et al11 |
| Caucasian          | 1.18  | .037    | Shiffman et al12 |
| American           | 1.29  | .004    | Shiffman et al13 |
| Canadian           | 0.85  | .176    | Stewart et al11 |
| European           | 0.99  | .729    |           |
| Hispanic           | 0.77  | .507    |           |
| African Americans  | 0.7   | .207    | Assims et al16 |
| East Asians        | 0.6   | .114    |           |
| South Asians       | 1.03  | .701    |           |
| Costaricans        | 1     | .98     | Bare et al17 |
| Western Indians    | 0.76  | .586    | Bhanushali et al29 |
| Han Chinese**      | 1.01  | .92     | Wu et al19 |
| South Indians      | 1.07  | .709    | Vishnupraphu et al30 |
| Saudi (Eastern province) | 0.93 | .598 | Our study |

Non-Association studies | | |

*OR calculated on Log additive mode of inheritance; ** Associated with non-fatal MI but not with CAD.

Asians, Hispanics and admixed cases and controls. The five large prospective studies (ARIC, CHS, WHS, CARE and WOSCOPS)10-13 that reported an association included patients with CAD broadly defined by revascularization, MI, and cardiovascular death in contrast to the lack association in two case-control studies (OHGS, WTCCC)20,21 and one meta-analysis,19 which included patients with angiographically defined CAD. A possible explanation for the discrepancy is that both the meta-analyses incorporated data on a biased basis. Li et al (2010) pooled a total of seven studies which all reported an association between KIF6 719 Arg and CAD events.15 On the other hand, Assimes et al 2010 pooled data from 19 case-control studies that lacked the association.16

To date, more than eight genome-wide association studies have been conducted worldwide on CAD, dyslipidemia and MI from Canadian and primarily Europeans from the United Kingdom, Sweden and Italy, but no variant in KIF6 has yet emerged as a statistically significant marker.20-28 However, the role of this risk allele in the Saudi Arabian population is unknown. Stratification of CAD patients into MI and non-MI revealed that there is no statistically significant associa-
tion between the SNP and an increased risk of CAD. Similar findings were reported by Bhanushali et al for non-MI and MI CAD patient groups.29

The present case-control study demonstrates that the common KIF6 719Arg allele carriers from the Eastern Province of Saudi Arabia were not at a significantly higher risk for CAD and non-fatal MI. Our results corroborate the findings of other case-control studies17,29-31 shown in Table 7. We observed no convincing evidence of an association between CAD subjects in this ethnic group and the KIF6 Trp719Arg SNP. This could be due to a number of reasons, including ethnicity and other genetic factors which might play a role in CAD development in our population.

Although it has been reported that the use of statins will ameliorate the risk of coronary events in KIF6 719Arg carriers,17 the limitation of the present study is the unavailability of data on statin usage among the patient population.

In conclusion, carriers of the KIF6 719Arg allele did not have an increased risk of CAD and non-fatal MI among the population of the Eastern Province of Saudi Arabia. Additional country-wide studies should shed further light on the significance of the association of KIF6 719Arg polymorphism with CAD and contribute toward the elucidation of the role of kinesins in the pathogenesis of CAD.

**Competing Interests**
The author(s) declare that they have no competing interests.

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