1.a. Full Title: Association of KIF6 719Arg with CHD and MI in the Atherosclerosis Risk in Communities Study (ARIC)

b. Abbreviated Title (Length 26 characters): KIF6 and CHD

2. Writing Group:
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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. ML

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3. **Timeline**: All analyses will be carried out at the University of Texas Health Science Center at Houston under the supervision of Dr. Eric Boerwinkle. This SNP was genotyped in ancillary study 2004.11, analyses and manuscript preparation is projected to take place over the next 6 months.

4. **Rationale**: In four prospective cohorts, carriers of the risk allele (719Arg) of *KIF6* Trp719Arg SNP had an increased risk of MI or CHD. In the Cardiovascular Health Study (CHS), carriers had increased risk of incident MI in whites (HRR=1.29, P=0.005) and in African Americans (HRR=4.14, though not statistically significant, P=0.08)\(^1\). In the Women’s Health Study (WHS), carriers had an increased risk of incident CHD (HRR=1.24, P=0.013) as well as MI (HRR=1.34, P=0.034)\(^2\). In the placebo arm of the Cholesterol and Recurrent Events (CARE) study, carriers had an increased risk of incident MI (HRR=1.50, P=0.03) and in the placebo arm of the West of Scotland Coronary Prevention Study (WOSCOPS) carriers had an increased risk of incident CHD (HRR=1.55, P=0.005)\(^3\). In ARIC, the Arg allele (in an additive genetic model) was also shown to be associated with increased risk for incident CHD in white (HRR=1.09, P=0.05) and separately in African American (HRR=1.23, though not statistically significant, P=0.06) participants during an average of a 13 year follow-up period\(^4\)\(^-\)\(^5\). However, the association of *KIF6* 719 Arg carrier status (i.e. ArgArg or TrpArg vs TrpTrp) with incident CHD or MI in ARIC has not been analyzed.

A recent update of ARIC data includes follow-up information from baseline through to Dec. 31 of 2005. We therefore plan to investigate whether carrying the *KIF6* 719Arg allele (ArgArg or ArgTrp) is associated with increased risk of incident CHD, or incident MI, during the 16 year follow-up period in ARIC. We also plan to investigate whether the ARIC population provides any evidence that the association of *KIF6* carrier status with CHD or MI risk is different between whites and African Americans or between males and females.
5. **Main Hypothesis/Study Questions:**

**Main hypothesis:** Among the white and African American participants of ARIC during 16 years of follow-up, carriers compared with noncarriers of the risk allele (719Arg) of the *KIF6* Trp719Arg SNP have increased risk of CHD.

**Study questions:**

Main question: Among the white and African American participants of ARIC, did carriers of the risk allele of the *KIF6* Trp719Arg SNP have increased risk of incident CHD after adjusting for race (either as self reported or as represented by the first one or more principle components from a global admixture analysis) and traditional risk factors?

Exploratory analyses:

1. Among the white and African American participants of ARIC, did carriers of the risk allele of the *KIF6* Trp719Arg SNP have increased risk of incident MI?
2. Was there a significant interaction between race and *KIF6* carrier status for the time to first CHD event or for the time to first MI event?
3. Was there a significant interaction between sex and *KIF6* carrier status for the time to first CHD event or for the time to first MI event?

6. **Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).**

**Study design:** Prospective follow-up data through December 31, 2005 of all white and African American ARIC participants that were free of CHD or stroke at baseline will be used. The *KIF6* Trp719Arg SNP was genotyped as part of a collaboration between scientists at Celera and Dr. Boerwinkle as described in ARIC Ancillary Study 2004.11.

**Inclusions/exclusions:** The following ARIC participants were excluded: those who had a positive or unknown history of stroke or stroke symptoms, positive history or missing
data for CHD, African Americans not from Jackson, MS or Forsyth County, NC, race other than African American or white, and individuals with restricted DNA use. A total of 13,403 participants remained after these exclusions.

**Outcome:** The primary outcome measure is time to the first occurrence of a component of the CHD endpoint, i.e. definite or probable MI, silent MI between examinations ascertained by electrocardiogram, definite fatal CHD death, or coronary revascularization.

**Other variables of interest:** Other variables needed for this manuscript include time to the first occurrence of a component of the MI endpoint (i.e. definite or probable MI, silent MI between examinations ascertained by electrocardiogram, definite fatal MI), the first one or more principle components from a global admixture analysis, race, age, sex, systolic and diastolic blood pressure, hypertension medication use, total cholesterol, HDL-cholesterol, LDL-cholesterol, diabetes status, smoking status, and family history of CHD.

**Data analysis**

**Survival analyses:** Analyses will be carried out in combined white and African American participants of ARIC followed from baseline until the earliest of December 31, 2005, the date of last contact, or death. Incidence rates of CHD or MI will be calculated using person-time methods.

Carriers will be compared with noncarriers in Cox proportional hazard analyses and adjusted in Model 1 for sex, age, and race, or in Model 2, for sex, age, race, plus other traditional risk factors at baseline (systolic and diastolic blood pressure, hypertension medication use, total cholesterol, HDL-cholesterol, LDL-cholesterol, diabetes status, smoking status, and family history of CHD). As an alternative to adjusting for self reported race, the Cox proportional hazard analyses will be rerun in Model 1 and Model 2 with race replaced by the first one or more principle components from a global admixture
analysis. To test for an interaction between KIF6 carrier status and race or the principle components, the Cox model will include KIF6 carrier status, race or the principle components, and an interaction term for KIF6 carrier status and race or the principle components. To test for an interaction between KIF6 carrier status and sex, the Cox model will include KIF6 carrier status, sex, and an interaction term for KIF6 carrier status and sex.

**Power:** We will have approximately 84% or 45% power to detect the association of KIF6 carrier status with risk of incident CHD or incident MI among white and African American participants of ARIC if we assume a hazard ratio of 1.2 for carriers of the KIF6 risk allele.

7.a. Will the data be used for non-CVD analysis in this manuscript?  ____ Yes __x__ No

b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value RES_OTH = “CVD Research” for non-DNA analysis, and for DNA analysis RES_DNA = “CVD Research” would be used?  ____ Yes _____ No

(This file ICTDER03 has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript?  __x__ Yes ____ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 must be used to exclude those with value RES_DNA = “No use/storage DNA”?  __x__ Yes _____ No

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status. ARIC Investigators have access to the publications list under the Study Members Area of the web site at:  [http://www.csec.unc.edu/ARIC/search.php](http://www.csec.unc.edu/ARIC/search.php)

____x____ Yes ________ No

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?
Both of these manuscripts are part of this same ancillary study. Therefore, the investigators can assure lack of overlap or duplication.

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?  
   _x_ Yes   ____ No

11.b. If yes, is the proposal
   _x_ A. primarily the result of an ancillary study (2004.11)
   ____ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)*  __________)

*ancillary studies are listed by number at http://www.cscc.unc.edu/aric/forms/

12. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.

References:
2. Shiffman D, Chasman DI, Zee RY, Iakoubova OA, Louie JZ, Devlin JJ, Ridker PM. A kinesin family member 6 variant is associated with coronary heart disease in the Women's Health Study. J Am Coll Cardiol. 2008;51:444-448
3. Iakoubova OA, Tong CH, Rowland CM, Kirchgessner TG, Young BA, Arellano AR, Shiffman D, Sabatine MS, Campos H, Packard CJ, Pfeffer MA, White TJ,
