Journal of the American College of Cardiology
Vol. 51, No. 22, 2008

ISSN 0735-1097/08/$34.00

CORRESPONDENCE

Letters to the Editor

Association of the 719Arg Variant of *KIF6* With Both Increased Risk of Coronary Events and With Greater Response to Statin Therapy

We read with interest the editorial comment (1) accompanying 3 reports that described the association of the 719Arg allele of *KIF6* with both increased risk of coronary heart disease and with response to statin treatment (2–4). However, we would like to comment on 2 assertions made in that evaluation of the work. The editorial stated that *KIF6* is not expressed in the vasculature. One would expect a gene with a biologically plausible role in coronary heart disease to be expressed in coronary arteries, and, in fact, *KIF6* is expressed in coronary arteries and other vascular tissue. A striking example of *KIF6* expression in human coronary arteries can be seen in the data generated by King et al. (5). Their data indicated that, in some human coronaries, *KIF6* is among the top 5% of overexpressed genes, based on a study of over 20,000 genes (see GEO accession number GDS1597 at http://www.ncbi.nlm.nih.gov/projects/geo/) .

The editorial also stated that the *KIF6* association studies were restricted to analysis of only 1 single nucleotide polymorphism (SNP) in the *KIF6* gene. In fact, Iakoubova et al. (2) reports an analysis of 26 additional SNPs in a 95.5-kb interval of Chr 6 that surrounds the *KIF6* Trp719Arg SNP. These 26 additional SNPs could also be considered surrogates (or tagging SNPs) for 117 additional SNPs in this interval.

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doi:10.1016/j.jacc.2008.02.061

Please note: Dr. Iakoubova has employment and ownership interest for Celera; Dr. Shepherd is on the Speakers' Bureau for AstraZeneca, Pfizer, and Sankyo and is a consultant for AstraZeneca, Pfizer, and GlaxoSmithKline; and Dr. Sacks was an expert witness for Pfizer and is a consultant for Bristol-Myers Squibb.

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Reply

I thank Dr. Iakoubova and colleagues for the information (1–4). They cite King et al. (5), who described detection of messenger ribonucleic acid (mRNA) expression by microarray in coronary segments isolated from explanted hearts of 22 patients, mostly with ischemic heart disease. The main findings were decreased expression levels of smooth muscle cell genes and increased levels of immune/inflammatory markers. However, I did not find any reference to *KIF6* (5). The microarray data, which requires validation by another technique, is posted at NCBI-GEO at http://www.ncbi.nlm.nih.gov/sites/entrez. It shows increased mRNA levels of *KIF6* in some coronary segments but reduced or unchanged levels in others. The data do not specify expression of *KIF6* in normal coronaries, a prerequisite for establishing the causality, as the cause (expression) has to precede the effect. Dr. Iakoubova and colleagues indicate that they analyzed 26 additional single nucleotide polymorphisms (SNPs) at the *KIF6* locus in 1 of the 3 study populations. All were in linkage disequilibrium (LD) not only with the Trp719Arg but also with 117 additional SNPs. In this scenario, Trp719Arg may not be the true susceptibility SNP or *KIF6* the true risk gene. The LD structure of the region should be analyzed, preferably in all 3 study populations, to identify other putative candidates. Mechanistic studies are necessary to distinguish the true susceptibility allele (gene) from those in LD with the risk allele (gene).

The most important impact of the findings, if proven to be true, would be in implicating a new pathway for the pathogenesis of coronary atherosclerosis and, hence, novel therapeutic targets. Most susceptibility alleles for complex traits, because of a small effect size on absolute risk, are unlikely to portend meaningful impact on pre-clinical diagnosis, early risk stratification, early intervention, prognostication, or individualization of therapy. Dr. Iakoubova and colleagues have a tremendous opportunity to rise to the challenge by delineating the molecular mechanism(s) by which Try719Arg in *KIF6* predisposes to coronary atherosclerosis, its clinical complications, or response to statins. By doing so, they could make an endurable impact in the care of millions of people worldwide. Otherwise, I humbly submit that the findings are unlikely to fulfill the late Dr. Koshland's Cha-Cha-Cha theory of scientific discoveries (6).

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