The KIF6 Collapse*

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Over the past 2 years, the Celera Corporation (Alameda, California) has heavily marketed its KIF6 Trp719Arg variant assay to cardiologists and primary care physicians. To date, >160,000 tests have been ordered in the U.S. alone at a cost of approximately $100 per test (1). Most recently, Celera has licensed 3 laboratories in Germany with plans to extend KIF6 testing internationally within a year. The genomic basis for this assay stems primarily from a few observational studies of cohorts that demonstrated a modest increase in risk of coronary artery disease (CAD) in European carriers of the common KIF6 719Arg variant allele (odds ratio [OR]: 1.1 to 1.5) (2–4). Interestingly, the PROVE IT–TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy in Myocardial Infarction–Thrombolysis In Myocardial Infarction 22) trial further demonstrated that therapy with statins abolished this increased risk in those individuals with the KIF6 variant allele (2). These studies have formed the foundation for Celera’s “Statincheck,” which has been promoted as a rapid pharmacogenetic assay that identifies individuals who will most likely benefit from statin therapy (1).

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Now, Assimes et al. (5) in this issue of the Journal report results from a very important study strongly refuting the KIF6 link to CAD in a well-conducted and elegant meta-analysis involving >17,000 cases of CAD and >39,000 controls from 19 different studies conducted around the world. An independent analysis of the early-onset myocardial infarction (MI) cohort and diverse ancestries also failed to reveal any significant correlation between KIF6 and CAD. Notably, 12 of the 19 studies included in the analysis only enrolled cases with a documented history of MI, a much more clinically robust and distinct phenotype than the more commonly used CAD (6). Further, 14 of the studies also restricted enrollment to individuals with early-onset disease (women 65 years of age and younger, men 55 years of age and younger). The vital inclusion of these genetically enriched populations substantially enhances the power of their meta-analysis for detecting any potential genetic link between KIF6 and CAD risk and greatly limits the potential of their results being falsely negative (6).

So what went wrong? Why have >150,000 KIF6 genotypes been ordered in the past 2 years for a test that now seems to be useless? Closer inspection of the original data implicating KIF6 yields several clear explanations. Foremost, the original observational studies used to “firmly” establish the KIF6 variants association with CAD used antiquated candidate gene-based methodologies (2–4), a method well-known to be plagued by false-positive results and a notorious inability for variants originally identified to be subsequently validated in additional studies (also known as winner’s curse) (7). To further add to existing skepticism about KIF6 is the lack of mechanistic studies demonstrating the gene’s impact on atherosclerosis, lipid metabolism, CAD, or MI (8,9). Of note, the authors of the current study appropriately emphasize that “no consistent expression of this gene has been demonstrated in relevant tissues such as the vasculature” (8,9).

Today, enabled by the International Human HapMap consortium, we are able to simultaneously assay for >500,000 common (present in >5% of the population) single nucleotide polymorphisms (SNPs) in genome-wide association studies (GWASs) for the purpose of identifying, in an unbiased manner, genetic markers of complex trait susceptibility that reach stringent statistical significance thresholds (p ≤ 5 × 10^-8) (10). Beyond this, replication in independent cohorts is required before such evidence of genome-wide significance of a marker can be considered validated. This approach, unlike previous candidate gene methods, has provided incontrovertible evidence of novel CAD susceptibility variants (6,10). In particular, common SNPs in apolipoprotein E, lipoprotein(a), chromosome 9p21, and many other regions of the genome have been identified and validated as CAD susceptibility markers in multiple GWASs involving thousands of CAD cases and controls (11–16). Further, the clear functional significance of lipoprotein(a) and apolipoprotein E in pathways of lipid metabolism bolsters existing GWAS evidence and supports their link to common forms of CAD and MI. In contrast, no variant in KIF6 has yet emerged as a statistically significant marker in >8 GWASs conducted to date on dyslipidemia, CAD, and MI (11–13,15,17–20). Such a common variant (present in >35% of Europeans) should have clearly surfaced in these GWASs if the association was truly valid. In addition, all SNP arrays used in these studies directly genotyped the at-risk KIF6 SNP—rs20455—and did not require imputation (Fig. 1). Therefore, even before the publication of the current study, the association of

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rs20455 (present in >35% of Europeans) with CAD was arguably tenuous at best.

Proponents of KIF6 testing will almost certainly continue to argue that a high prevalence of statin use in the CAD cases may have abrogated the KIF6 risk of CAD, and, therefore, no significant effect for KIF6 was observed. However, that argument holds little merit. In fact, several of the initial reports noting the KIF6 association with CAD did not indicate that statin users were excluded or censored before their analysis (4,21,22). Further, given the >8,000 cases of early-onset disease included in the current analysis, statin use was most likely to be lower than in the initial studies used to establish the KIF6 variant as a novel “predictive” biomarker.

The final and decisive affront to the KIF6 story relates to the unraveling of its largely unsubstantiated claims that variant carriers exhibit an enhanced response to statin therapy. This premise is largely predicated on previous data linking KIF6 to a heightened risk of CAD. However, as the current study nicely demonstrates, this is not the case. Most importantly, no plausible biological mechanism of KIF6-mediated statin response is currently available. This is in direct contrast to hepatic cytochrome (CYP) 2C19 gene variants, which recently, through a GWAS on antiplatelet response to clopidogrel, have been found to be the only common variant yet identified for genomic resistance to this widely used agent (23). To date, no such GWAS assessing statin response has been conducted or even initiated. Until such studies are conducted, pharmacogenetic tests with claims of identifying statin hyper-responders or hyporesponders should be viewed with considerable skepticism. Since the initial draft of the human genome in 2001, we have witnessed a >14,000-fold decrease in the cost of DNA genotyping and sequencing (24). Accompanying this dramatic trend has been a greatly increasing number of loci linked to disease susceptibility and treatment response. Going forward, such genetic and pharmacogenetic markers must be accompanied by stringent vetting by investigators in well-designed, hypothesis-free, genome-wide studies before promoting their use in clinical practice. Although several cardiovascular-related genomic and pharmacogenomic biomarkers have clearly surpassed this important evidence threshold including the aforementioned apolipoprotein E, LPA, and the recently identified CYP2C19 variants involved in clopidogrel metabolism, the KIF6 association has lacked such data from the time of its initial reports. Going forward, the KIF6 story should serve as a valuable reminder of the potential pitfalls present in prematurely adopting a genomic test without sufficient evidence.

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