Medical Policy

BlueCross BlueShield of Kansas
An Independent Licensee of the Blue Cross and Blue Shield Association

Title: KIF6 Genotyping for Predicting Cardiovascular Risk and/or Effectiveness of Statin Therapy

Professional
Original Effective Date: March 10, 2011
Revision Date(s): June 5, 2012; January 15, 2013; May 10, 2013
Current Effective Date: March 10, 2011

Institutional
Original Effective Date: April 11, 2011
Revision Date(s): June 5, 2012; January 15, 2013; May 10, 2013
Current Effective Date: April 11, 2011

State and Federal mandates and health plan member contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. To verify a member's benefits, contact Blue Cross and Blue Shield of Kansas Customer Service.

The BCBSKS Medical Policies contained herein are for informational purposes and apply only to members who have health insurance through BCBSKS or who are covered by a self-insured group plan administered by BCBSKS. Medical Policy for FEP members is subject to FEP medical policy which may differ from BCBSKS Medical Policy.

The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents of Blue Cross and Blue Shield of Kansas and are solely responsible for diagnosis, treatment and medical advice.

If your patient is covered under a different Blue Cross and Blue Shield plan, please refer to the Medical Policies of that plan.

DESCRIPTION

Genetic testing to determine the *KIF6* Trp719Arg variant status of patients is being evaluated as a prognostic test to predict risk of future cardiovascular events and/or as a pharmacogenetic test to predict response to statin therapy, particularly in high-risk patients.

Background

Analysis of prospective observational studies of cardiovascular health, and of the placebo arm of randomized controlled trials (RCTs) of statin intervention in at-risk populations have suggested a significant association between the Trp719Arg single nucleotide polymorphism (SNP; rs20455) in kinesin-like protein 6 (*KIF6*) and the development of clinical coronary artery disease (CAD). Approximately 60 % of the population carries the

putative *KIF6* high-risk 719Arg allele. Moreover, carriers of the 719Arg allele in the treatment arms of the statin trials appeared to be at no increased risk, or at decreased risk of CAD or recurrent myocardial infarction (MI), depending on the intensity of the statin therapy. These results supported the development of a *KIF6* Trp719Arg genotyping test for use as a predictor of CAD risk and of the likely effectiveness of statin therapy.

Celera Corporation, now a wholly owned subsidiary of Quest Diagnostics, Inc., holds a U.S. patent relating to methods of determining heart attack risk by detecting the *KIF6* gene variant and reduction of such increased risk by statin therapy. Celera's Berkeley HeartLab subsidiary has been offering *KIF6* genotyping (*KIF6*-StatinCheck™ Genotype Test) since July 2008. San Francisco General Hospital's Clinical Chemistry Laboratory (University of California, San Francisco), is the only non-Celera lab to obtain a license to develop a *KIF6* LTD; a small number of clinical labs/health care groups have negotiated with Celera to offer the test by sending it to BHL (e.g., Aurora Health Care of Milwaukee, WI).

Regulatory Status

The *KIF6* genotyping test is not a manufactured test kit and has not been reviewed by the U.S Food and Drug Administration (FDA). Rather, it is a laboratory-developed test (LTD), offered by clinical laboratories licensed under Clinical Laboratory Improvement Amendments (CLIA) for high-complexity testing. The company submitted a Premarket Approval application to the FDA in January, 2011, for their KIF6 Genotyping Assay performed on Abbott's m2000™ instrument system. However, on April 7, the FDA sent a letter to Celera indicating that its application is not approvable "without major amendment." The data and publications submitted were deemed "insufficient to demonstrate the safety and effectiveness of the device for its proposed intended use." The agency indicated that additional data on clinical utility may be required, which could include conducting a randomized controlled clinical trial. As of the current update, there appears to be no further action on this front.

POLICY

KIF6 Genotyping is considered **experimental / investigational** for predicting cardiovascular risk and/or the effectiveness of statin therapy.

Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

RATIONALE

Literature Review

The KIF6 protein belongs to the kinesin superfamily of proteins involved in intracellular transport. The exact function of the *KIF6* gene product is as yet undetermined. According to one article, the gene is not expressed in the vasculature, the primary site of atherosclerosis. Rather, it is expressed in low levels in the brain, connective tissue, colon, eye, pharynx, skin, and testes. (1) In contrast, a study presented at the American Heart Association Arteriosclerosis, Thrombosis and Vascular Biology 2010 Scientific Sessions reported data derived from tissue immunohistochemistry, locating KIF6 protein in macrophages surrounding neovessels and in foam cells in human atherosclerotic lesions. (2) Nevertheless, there is as yet no strong evidence that KIF6 protein plays a biological role in atherosclerosis, lipid metabolism, coronary artery disease (CAD), or myocardial infarction (MI).

Clinical validity

The Trp719Arg single nucleotide polymorphism (SNP) in the *KIF6* gene was deliberately investigated and associated with CAD outcomes in retrospective evaluations of prospective, observational studies (Table, Part 1), (3-5) and in retrospective evaluations of the placebo arms of randomized, controlled trials (RCTs) of statin therapy (Table, Part 2). (6, 7) Whether the initial inclusion of *KIF6* markers in early studies initiated by Celera was based on candidate gene selection or on larger, gene-scanning studies is unclear from the published literature, and claims of critics and test developers on this point are contradictory.

In both relatively unselected prevention cohorts (Table, Part 1), and in trial populations selected for high risk of a CHD event, the Trp719Arg SNP is significantly associated with coronary heart disease (CHD) outcomes at hazard ratios (HR) in the range of approximately 1.1 to 1.5.

In the statin treatment arms of RCTs, carriers of the 719Arg variant were at decreased risk of an event compared to controls, whereas non-carriers appeared to derive little if any benefit from statin treatment. In the analysis of the Pravastatin or Atorvastatin Evaluation and Infection Therapy: Thrombolysis in Myocardial Infarction 22 trial, which compared less intensive (pravastatin) versus more intensive (atorvastatin) therapy, carriers of the 719Arg variant received significantly greater benefit from intensive therapy than noncarriers. (8)

However, a large meta-analysis of 19 case-control studies (Table, Part 3) (9) found no association between the Trp719Arg SNP and CAD, even when the overall population was restricted to Europeans with early onset disease (less likely to be confounded by statin therapy), to Europeans with myocardial infarction (MI), or to Europeans with early onset MI. The authors of the meta-analysis note that they examined only non-fatal MI; if the Trp719Arg variant increases the risk of fatal CAD more than the risk of non-fatal CAD, the study results could be biased toward the null. The meta-analysis could not examine whether the effect on risk was modified by statin therapy.

In addition to the findings of the meta-analysis, none of the several, large genome-wide association studies for CAD or MI reported any SNPs at the *KIF6* locus as significant.(10-14) For this reason, some have considered the possible candidate (i.e., pre-selected) gene approach to the *KIF6* variant analysis by the test developers as potentially flawed, given the current lack of biologic plausibility.

The most recently published evidence (Table, Part 4) is consistent with the meta-analysis results. Ridker et al. (15) evaluated the effect of the *KIF6* variant on the outcomes of 8,781 Caucasian trial participants in the JUPITER (Justification for Use of Statins in Primary Prevention, An Intervention Trial Evaluating Rosuvastatin) study and in the trial as a whole. Rosuvastatin was equally effective at reducing cardiovascular event rates among carriers and noncarriers of the *KIF6* variant; results for trial participants as a whole were essentially identical. Hopewell et al. (16) evaluated data from the Heart Protection Study on more than 18,000 patients with prior cardiovascular disease or high predisposing risk and compared outcomes after treatment with simvastatin or placebo. The authors reported no association of *KIF6* variant status with outcome in the placebo arm, nor in the treatment arm—simvastatin reduced the incidence of coronary events equally regardless of *KIF6* status. Hoffmann et al. (17) evaluated a narrowly focused population of patients with type 2 diabetes and less than 2 years of previous treatment by hemodialysis, randomly assigned to double-blinded treatment with either 20 mg of atorvastatin (n=619) or placebo (n=636). In neither the placebo nor the statin group was there any association of *KIF6* genotype with major cardiovascular events. This study was limited because statins did not achieve the expected improvement in survival despite significantly decreasing low-density lipoprotein (LDL) cholesterol. Nevertheless, taken together, these 3 studies show that in different populations with different levels of vascular risk and treated with different statin drugs, there was no measureable effect of the *KIF6* variant on statin response nor any association with vascular risk.

Another recent study, by Arsenault et al. (18) investigated whether carriers of the *KIF6* variant obtain more benefit from high-dose statin therapy than do noncarriers by retrospective analysis of 2 prospective trials. In the Treating to New Targets (TNT) study, 4,599 patients with stable coronary heart disease (CHD) and LDL cholesterol levels <130 mg/dL, randomly assigned to receive either 10- or 80-mg of atorvastatin per day and followed up for a median of 4.9 years, were genotyped. *KIF6* genotype did not affect risk for future events within treatment arms. Genotype subgroups had a similar benefit from 80 mg atorvastatin compared to 10 mg, except for the homozygous variant subgroup, which was the only group with a statistically significant benefit from the higher statin dose, but interaction for genotype by treatment was not significant. The Incremental Decrease in End Points Through Aggressive Lipid-Lowering (IDEAL) study enrolled patients with a history of MI and randomized them to high-dose atorvastatin or usual dose simvastatin and followed them for a median of 4.8 years. Of the 8,888 enrolled, 6,541 were genotyped; there were no significant differences by *KIF6* genotype in comparative response to statin treatment, and the interaction for genotype by treatment was not significant.

A retrospective evaluation of PROSPER (PROspective Study of Pravastatin in the Elderly at Risk) trial participants found a significant relationship between *KIF6* variant homozygotes and fatal or non-fatal myocardial infarction or stroke only in women on pravastatin (see Table), which lost significance after correction for multiple comparisons. (19) The study authors also reported that homozygous carriers of the *KIF6* variant were significantly less responsive to pravastatin, but did not recommend the use of *KIF6* testing to determine statin use.

The conflicting results regarding the *KIF6* variant, CHD, and treatment outcomes appears to have been explained in a meta-analysis by Ference et al. (20) The authors included 37 case-control studies, prospective cohort studies, or randomized trial treatment allocation arms (each considered as a separate cohort), which together enrolled 144,931 participants and reported 27,465 CHD events, The *KIF6* genotype, and, in particular, the Trp719Arg SNP carrier status, was

not associated with increased risk of CHD event. A new analysis resulted in evidence of *KIF6* variant effect modification. For each mmol/L increase in LDL cholesterol, *KIF6* variant carriers experienced a 15% greater increase in the relative risk of CHD, as compared to non-carriers (ratio of risk ratio [RR]: 1.15, 95% confidence interval [CI]: 1.06–1.25, p=0.001). Similarly, the decrease in risk for each mmol/L decrease in LDL was 13% greater for variant carriers. Also included in the meta-analysis were 8 randomized trials of statin therapy, involving 50,060 participants and 7,307 CHD events. *KIF6* variant carriers derived a greater clinical benefit for each mmol/L reduction in LDL cholesterol during treatment with a statin than did non-carriers (ratio of RR: 0.87, 95% CI: 0.77–0.99, p=0.038). Thus, the results suggest that the *KIF6* Trp719Arg variant increases vulnerability to LDL cholesterol. This might explain why *KIF6* variant carriers appear to derive greater clinical benefit from a statin even though the variant does not appear to affect the ability of the statin to lower LDL cholesterol, nor does it appear, on average, to be independently associated with the risk of CHD. However, "the association between the *KIF6* variant and the risk of CHD will vary according to the average LDL cholesterol level of the population(s) under study." (20) This may help explain some of the conflicting reports of KIF6 genotype association with CHD.

Clinical utility

Based on the earlier retrospective analyses of statin trials, and the apparent association of the Trp719Arg variant with treatment benefit, genotyping was recommended to predict which patients would most benefit from pravastatin or atorvastatin treatment. For carriers of the *KIF6* variant, the number needed to treat (NNT) to prevent 1 event is approximately 10 to 20, whereas for non-carriers, the NNT is approximately 80 to more than 100.(21) Thus, it has been suggested that for patients at clinically high risk who are non-carriers, additional intervention may be appropriate; for variant carriers at clinically lower risk who might not normally be treated, statin treatment may provide greater than average benefit. However, these management changes have not been tested prospectively. The more recent retrospective evaluations of prospective, randomized trials (Table, part 4), conducted in large patient populations, indicate that noncarriers of the KIF6 variant benefit from statin therapy to the same degree as variant carriers, likely invalidating the rationale for genotyping and basing statin treatment recommendations on the test result. (22)

Celera has been working with pharmacy benefit manager Medco to generate real-world evidence regarding patient knowledge of *KIF6* genotype status and statin compliance. A prospective study has already completed enrollment (NCT01068834; Additional KIF6 Risk Offers Better Adherence to Statins, or AKROBATS, trial) and will compare statin adherence in those who learn about their carrier status versus those who do not. Preliminary data were reported at the 2011 American Society of Human Genetics annual meeting; the authors indicated that patients taking statins were more likely to take their medications if they had been tested for the *KIF6* variant. Conclusions await completion of the trial and full publication.

Summary

The data supporting the association of the *KIF6* Trp719Arg single nucleotide polymorphism (SNP) with coronary artery disease (CAD) outcomes are contradictory. The most recent evidence from large populations at different levels of vascular risk does not support a significant association with future CAD outcomes. Moreover, the biologic function of the KIF6 protein is currently unknown. Thus, the clinical validity for the *KIF6* genotyping test has not been shown. The most recent analyses of treatment trials indicate that the efficacy of statin treatment appears to be similar in

carriers and non-carriers of the mutation. A large meta-analysis shows that *KIF6* variant carriers derive greater clinical benefit from low-density lipoprotein (LDL) cholesterol reduction compared to non-carriers by about 13%. It has not been determined whether knowledge of carrier status can be used to improve patient management decisions and improve outcomes. Thus, testing for *KIF6* status to determine statin treatment benefit is considered investigational.

Table. Results of individual studies investigating differential effects of KIF6 genotype on cardiovascular outcomes and Meta-analysis of the association of KIF6 with CAD outcomes.

Study	Patients Evaluated	KIF6 Association Evaluated	Results: Observational Study or Placebo Arm, KIF6V carriers vs. non-carriers	Results: Statin Arm vs. Placebo Arm (unless otherwise stated)
Part 1 KIF6 variant association with CAD outcomes in retrospective evaluations of prospective, observational studies				
Morrison et al. 2007 Retrospective evaluation of ARIC study (3)	U.S. individuals aged 45–64 years	MI, CHD death, or coronary revascularization	HR: 1.09 (95% CI,1.00-1.19)	N/A
Shiffman et al., 2008 Retrospective evaluation of CHS (5)	Adults aged 65 years and older	Incident M	HR: 1.29 (90% CI, 1.1-1.52)* (95% CI, 1.06-1.6)**	N/A
Shiffman et al., 2008 Retrospective evaluation of WHS (4)	Healthy Caucasian American women	Incident CHD event (MI, coronary revascularization, or CV-related death) or incident ischemic stroke	CHD HR: 1.24 (95% CI, 1.04-1.46) MI HR: 1.34 (95% CI, 1.02-1.75) Stroke HR: not sig.	N/A
Part 2 KIF6 variant association with CAD outcomes in retrospective evaluations of randomized, controlled trials of statin therapy				
Iakoubova et al., 2008 Retrospective evaluation of CARE study (7)	Caucasian MI survivors with total cholesterol <240 mg/dL	Recurrent fatal or non-fatal MI	HR: 1.50 (95% CI, 1.05-2.15)	Among KIF6V carriers: HR: 0.63 (0.46–0.87) Among non-carriers: HR: 0.80 (0.52–1.24)
Shiffman et al., 2010 Retrospective evaluation of CARE study (23)	MI survivors (all ethnicities) with total cholesterol <240 mg/dL	Recurrent fatal or non-fatal MI		Adjusted for self-reported ethnicity, Among KIF6V carriers: HR: 0.63 (0.49-0.83) Among non-carriers: HR: 1.01 (0.69-1.45)
Iakoubova et al., 2008 Nested case-control study from WOSCOPS trial (7)	Men with hyper-cholesterolemia but no history of MI	Nonfatal MI, revascularization procedures, or death from CHD	OR: 1.55 (95% CI, 1.14-2.09)	Among KIF6V carriers: HR: 0.50 (0.38–0.68) Among non-carriers: HR: 0.91 (0.64–1.28)
Iakoubova et al., 2008 Retrospective evaluation of PROVE IT-TIMI 22 (8)	Patients hospitalized for MI or high-risk unstable angina	Composite endpoint: all-cause mortality, MI, unstable angina, or stroke	(no placebo arm)	Intensive vs. moderate statin therapy arms among: KIF6V carriers HR: 0.59 (0.45-0.77), Non-KIF6V carriers HR: 0.94 (0.70-1.27)
Iakoubova et al., 2010 Retrospective evaluation of PROSPER study (6)	Older patients with preexisting vascular disease	Composite endpoint: death from CHD, nonfatal MI, or fatal/ nonfatal stroke	HR: 1.28 (95% CI, 0.98-1.69)	Among KIF6V carriers: HR: 0.66 (0.52-0.86) Among non-carriers: HR: 0.94 (0.69-1.28)
	Older patients at increased risk for vascular disease			No benefit

Part 3 Meta-analysis of KIF6 variant association with CAD outcomes				
Assimes et al., 2010 Meta-analysis of 19 case-control studies(9)	(Various) 17,000 cases, 39,369 control	CAD cases with and without a diagnosis of non-fatal MI	OR: 0.98 (95% CI, 0.95-1.02)	N/A
	Europeans, subgroup with very early onset disease	(as above)	OR: 0.99 (95% CI, 0.94-1.04)	N/A
	Europeans, restricting cases to MI	(as above)	OR: 0.99 (95% CI, 0.96-1.03)	N/A
	Europeans, restricting cases to early onset MI	(as above)	OR: 1.03 (95% CI, 0.98-1.09)	N/A
Part 4 Recent publications				
Ridker et al., 2011 Retrospective evaluation of prospective JUPITER study (15) Rosuvastatin vs. placebo	Men and women free of diabetes or prior cardiovascular disease	Composite: CV death, nonfatal MI, nonfatal stroke, hospitalization for unstable angina, or arterial revascularization	HR=0.91 (95% CI, 0.66-1.26)	Among KIF6V carriers: HR:0.61 (0.43-0.87) Among non-carriers: HR:0.59 (0.39-0.88) P-interact=0.90
Hopewell et al., 2011 Retrospective evaluation of prospective Heart Protection Study (16) Simvastatin vs. placebo	Individuals at high risk for or a previous diagnosis of CV disease	Composite: CHD death, nonfatal MI, strokes, coronary or noncoronary revascularizations	No significant effect on risk of major CV events, regardless of modeling approach (p= 0.54 to 0.76)	Among KIF6V carriers: 23% (16% - 29%) Among non-carriers: 24% (17% - 31%) P-interact=0.4 to 0.7
Hoffmann et al., 2011 Retrospective evaluation of 4D prospective study (17) Atorvastatin vs. placebo	Patients with T2DM and <2 year prior hemodialysis treatment	Composite: death from cardiac causes, MI, or stroke	HR=0.83 (95% CI, 0.66–1.05)	Among statin-treated, KIF6V carriers vs. non-carriers: HR=0.96 (0.76–1.23)
Arsenault et al. 2011 Retrospective evaluation of prospective TNT (80 vs. 10 mg/day atorvastatin) and IDEAL (80 mg/day atorvastatin vs. 20-40 mg/day simvastatin) studies (18)	TNT: patients with stable CHD and LDL-C levels<130 mg/dL	Composite: coronary death, nonfatal MI, resuscitation after cardiac arrest and fatal or nonfatal stroke		Among KIF6V carriers: 0.85 (0.66-1.11) Among homozygote carriers: 0.44 (0.23-0.84) Among non-carriers: 0.81 (0.59-1.11) P-interact=0.81
	IDEAL: patients with a history of MI			Among KIF6V carriers: 0.91 (0.58-1.43) Among homozygote carriers: 0.88 (0.62-1.07) Among non-carriers: 0.85 (0.67-1.10) P-interact=0.91
Akao et al. 2012 Retrospective study of participants in PROSPER (PROspective Study of Pravastatin in the Elderly at Risk) trial, randomized to pravastatin 40 mg/day or placebo	Individuals with a history of, or risk factors for, vascular disease	MI or stroke	Homozygote HR=0.47, p=0.03 For women on pravastatin only; not significant after correction for multiple comparisons	

Abbreviations: CAD, coronary artery disease; CHD, coronary heart disease; CV, cardiovascular; MI, myocardial infarction; T2DM, type 2 diabetes mellitus; OR, odds ratio; HR, hazard ratio; CI, confidence interval; N/A, not applicable; MI, myocardial infarction; ARIC, Atherosclerosis Risk in Communities cohort; CHS, Cardiovascular Health Study; CARE, Cholesterol and Recurrent Events trial; WOSCOPS, West of Scotland Coronary Prevention Study; PROVE IT-TIMI 22, Pravastatin or Atorvastatin Evaluation and Infection Therapy: Thrombolysis in Myocardial Infarction 22 trial; WHS, Women's Health Study; PROSPER, PROspective Study of Pravastatin in the Elderly at Risk; JUPITER, Justification for Use of Statins in Primary Prevention, An Intervention Trial Evaluating Rosuvastatin; TNT, Treating to New Targets; IDEAL, Incremental Decrease in End Points Through Aggressive Lipid-Lowering.

*Published.

**Calculated from published data.

Practice Guidelines and Position Statements

No reference to KIF6 was found in the 2010 American College of Cardiology Foundation/American Heart Association Practice Guideline for Assessment of Cardiovascular Risk in Asymptomatic Adults. (24, 25) For the current update, no relevant updated or additional guidelines were found.

Hayes, Inc./Hayes Genetic Test Evaluation team conducted an assessment of "KIF6 p.Trp719Arg Testing to Assess Risk of Coronary Artery Disease and/or Statin Response" and concluded that the evidence was insufficient to determine utility, due largely to lack of evidence supporting clinical utility.(26)

Ongoing Clinical Trials

The Additional KIF6 Risk Offers Better Adherence to Statins (AKROBATS) trial (available at online site ClinicalTrials.gov Identifier: NCT01068834) is sponsored by Medco Health Solutions, Inc. in collaboration with Celera and is currently enrolling patients by invitation only. The purpose of this study is to determine whether providing subjects their *KIF6* carrier status (and associated cardiovascular event risk) will improve adherence to statin medications. The results of this study have been announced by Medco but are not yet published. According to the press release, tested patients who were informed of their test result had significantly higher overall adherence to their statin treatment.

Funded under American Recovery and Reinvestment Act of 2009 (ARRA) Investments in Coronary Artery Disease, Brigham and Women's Hospital is conducting the Genetic Risk Stratification to Identify Individuals for Early Statin Therapy study (Project No. 1RC1HL099634-01). Goals of the study are to 1) test whether specific panels of genetic variants identify patients who experience a greater clinical benefit with statin therapy using retrospective data; and 2) test whether specific panels of genetic variants identify patients who experience a higher risk of statin-induced adverse effects in the same cohorts. This retrospective data analysis project was due to be completed in August, 2011 but no updated information has been found.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

CPT/HCPCS

81479 Unlisted molecular pathology procedure

- There is currently no specific CPT code for this testing. Beginning in 2013, the unlisted molecular pathology code (81479) would be reported.
- Prior to 2013, a combination of the molecular diagnostic CPT codes (83890-83912) or unlisted CPT code 84999 would have most likely been used. For example, one laboratory website listed the following codes for this test: 83891, 83892, 83896, 83898, 83903, 83912.

DIAGNOSIS

Experimental / investigational for all diagnoses related to this policy.

REVISIONS

03-10-2011	Policy added to the bcbsks.com web site.
06-05-2012	Description section updated
	Rationale section updated
	References updated
01-15-2013	In Coding section: ▪ Added CPT code: 81479 (effective 01-01-2013) ▪ Updated coding instructions to remove reference to 83890-83912 which are no longer effective as of 12-31-2012.
05-10-2013	Description section updated
	Rationale section updated
	In Coding section: ▪ Updated coding instructions
	References updated

REFERENCES

1. Marian AJ. Surprises of the genome and "personalized" medicine. J Am Coll Cardiol 2008; 51(4):456-8.
2. Rosenfeld ME, Preusch M, Shiffman D et al. KIF6, an emerging coronary heart disease risk marker expressed by macrophages in atherosclerotic lesions in humans and mice. American Heart Association Arteriosclerosis, Thrombosis and Vascular Biology Scientific Sessions 2010; P692.
3. Morrison AC, Bare LA, Chambless LE et al. Prediction of coronary heart disease risk using a genetic risk score: the Atherosclerosis Risk in Communities Study. Am J Epidemiol 2007; 166(1):28-35.
4. Shiffman D, Chasman DI, Zee RY et al. A kinesin family member 6 variant is associated with coronary heart disease in the Women's Health Study. J Am Coll Cardiol 2008; 51(4):444-8.
5. Shiffman D, O'Meara ES, Bare LA et al. Association of gene variants with incident myocardial infarction in the Cardiovascular Health Study. Arterioscler Thromb Vasc Biol 2008; 28(1):173-9.
6. Iakoubova OA, Robertson M, Tong CH et al. KIF6 Trp719Arg polymorphism and the effect of statin therapy in elderly patients: results from the PROSPER study. Eur J Cardiovasc Prev Rehabil 2010; 17(4):455-61.
7. Iakoubova OA, Tong CH, Rowland CM et al. Association of the Trp719Arg polymorphism in kinesin-like protein 6 with myocardial infarction and coronary heart disease in 2 prospective trials: the CARE and WOSCOPS trials. J Am Coll Cardiol 2008; 51(4):435-43.
8. Iakoubova OA, Sabatine MS, Rowland CM et al. Polymorphism in KIF6 gene and benefit from statins after acute coronary syndromes: results from the PROVE IT-TIMI 22 study. J Am Coll Cardiol 2008; 51(4):449-55.
9. Assimes TL, Holm H, Kathiresan S et al. Lack of association between the Trp719Arg polymorphism in kinesin-like protein-6 and coronary artery disease in 19 case-control studies. J Am Coll Cardiol 2010; 56(19):1552-63.
10. Samani NJ, Erdmann J, Hall AS et al. Genomewide association analysis of coronary artery disease. N Engl J Med 2007; 357(5):443-53.
11. Kathiresan S, Voight BF, Purcell S et al. Genome-wide association of early-onset myocardial infarction with single nucleotide polymorphisms and copy number variants. Nat Genet 2009; 41(3):334-41.

12. McPherson R, Pertsemlidis A, Kavaslar N et al. A common allele on chromosome 9 associated with coronary heart disease. Science 2007; 316(5830):1488-91.
13. Helgadottir A, Thorleifsson G, Manolescu A et al. A common variant on chromosome 9p21 affects the risk of myocardial infarction. Science 2007; 316(5830):1491-3.
14. Wellcome Trust Case Control Consortium. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. Nature 2007; 447(7145):661-78.
15. Ridker PM, MacFadyen JG, Glynn RJ et al. Kinesin-like protein 6 (KIF6) polymorphism and the efficacy of rosuvastatin in primary prevention. Circ Cardiovasc Genet 2011; 4(3):312-7.
16. Hopewell JC, Parish S, Clarke R et al. No impact of KIF6 genotype on vascular risk and statin response among 18,348 randomized patients in the heart protection study. J Am Coll Cardiol 2011; 57(20):2000-7.
17. Hoffmann MM, Marz W, Genser B et al. Lack of association between the Trp719Arg polymorphism in kinesin-like protein-6 and cardiovascular risk and efficacy of atorvastatin among subjects with diabetes on dialysis: The 4D study. Atherosclerosis 2011; 219(2):659-62.
18. Arsenault BJ, Boekholdt SM, Hovingh GK et al. The 719Arg variant of KIF6 and cardiovascular outcomes in statin-treated, stable coronary patients of the treating to new targets and incremental decrease in end points through aggressive lipid-lowering prospective studies. Circ Cardiovasc Genet 2012;5(1):51-7.
19. Akao H, Polisecki E, Kajinami K et al. KIF6, LPA, TAS2R50, and VAMP8 genetic variation, low density lipoprotein cholesterol lowering response to pravastatin, and heart disease risk reduction in the elderly. Atherosclerosis 2012; 220(2):456-62.
20. Ference BA, Yoo W, Flack JM et al. A common KIF6 polymorphism increases vulnerability to low-density lipoprotein cholesterol: two meta-analyses and a meta-regression analysis. PloS one 2011; 6(12):e28834.
21. Li Y, Iakoubova OA, Shiffman D et al. KIF6 polymorphism as a predictor of risk of coronary events and of clinical event reduction by statin therapy. Am J Cardiol 2010; 106(7):994-8.
22. Musunuru K. Lack of association of KIF6 genotype with vascular disease and statin response. Circ Cardiovasc Genet 2011; 4(4):467-8.
23. Shiffman D, Sabatine MS, Louie JZ et al. Effect of pravastatin therapy on coronary events in carriers of the KIF6 719Arg allele from the cholesterol and recurrent events trial. Am J Cardiol 2010; 105(9):1300-5.
24. Greenland P, Alpert JS, Beller GA et al. 2010 ACCF/AHA Guideline for Assessment of Cardiovascular Risk in Asymptomatic Adults: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2010; 122(25):e584-636.
25. Greenland P, Alpert JS, Beller GA et al. 2010 ACCF/AHA Guideline for Assessment of Cardiovascular Risk in Asymptomatic Adults: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2010; 56(25):e50-103..
26. Allingham-Hawkins D, Lea A, Levine S. KIF6 p.Trp719Arg Testing to Assess Risk of Coronary Artery Disease and/or Statin Response. PLoS Curr 2010; 2:RRN1191.