Journal of the American College of Cardiology
© 2013 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 61, No. 9, 2013
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2012.10.051

Association Between the Chromosome 9p21 Locus and Angiographic Coronary Artery Disease Burden

A Collaborative Meta-Analysis

Kenneth Chan, MPHARM,* Riyaz S. Patel, MD,*†‡ Paul Newcombe, PHD,§ Christopher P. Nelson, PHD,‖ Atif Qasim, MD,¶ Stephen E. Epstein, MD,# Susan Burnett, PHD,# Viola L. Vaccarino, MD, PHD,** A. Maziar Zafari, MD, PHD,** Svati H. Shah, MD,†† Jeffrey L. Anderson, MD,‡‡ John F. Carlquist, PHD,‡‡ Jaana Hartiala, MS,†† Hooman Allayee, PHD,†† Kunihiko Hinohara, PHD,‖‖ Bok-Soo Lee, PHD,¶¶ Anna Erl, MD,## Katrina L. Ellis, PHD,*** Anuj Goel, PHD,††† Arne S. Schaefer, PHD,‡‡‡ Nour Eddine El Mokhtari, MD,‡‡‡§§§ Benjamin A. Goldstein, PHD,‖‖‖ Mark A. Hlatky, MD,‖‖‖ Alan S. Go, MD,¶¶¶ Gong-Qing Shen, MD, PHD,### Yan Gong, PHD,**** Carl Pepine, MD,**** Ross C. Laxton, BSC,* John C. Whittaker, PHD,†††† W.H. Wilson Tang, MD, PHD,†††† Julie A. Johnson, PHARMD,**** Qing K. Wang, PHD, MBA,### Themistocles L. Assimes, MD, PHD,‖‖‖ Ute Nöthlings, PHD,‡‡‡‡ Martin Farrall,†††§§§§ Hugh Watkins, MD, PHD, FMEDSCI,†††§§§§ A. Mark Richards, MD, PHD,*** Vicky A. Cameron, PHD,*** Axel Muendlein, PHD,¶¶¶¶ Heinz Drexel, MD,¶¶¶¶ Werner Koch, PHD,## Jeong Euy Park, MD, PHD,¶¶ Akinori Kimura, MD, PHD,‖‖ Wei-feng Shen, PHD,#### Iain A. Simpson, MD,***** Stanley L. Hazen, MD, PHD,‡‡‡‡ Benjamin D. Horne, PHD, MPH,‡‡ Elizabeth R. Hauser, PHD,†† Arshed A. Quyyumi, MD,‡ Muredach P. Reilly, MB,¶ Nilesh J. Samani, MD, FMEDSCI,‖ Shu Ye, MD, PHD*

London, Cardiff, Cambridge, Leicester, Oxford, and Southampton, United Kingdom; Atlanta, Georgia; Philadelphia, Pennsylvania; Washington DC; Durham, North Carolina; Salt Lake City, Utah; Los Angeles, Stanford, and Oakland, California; Tokyo, Japan; Seoul, Republic of Korea; Munich, Kiel, and Rendsburg, Germany; Christchurch, New Zealand; Cleveland, Ohio; Gainesville, Florida; Feldkirch, Austria; and Shanghai, China

Objectives This study sought to ascertain the relationship of 9p21 locus with: 1) angiographic coronary artery disease (CAD) burden; and 2) myocardial infarction (MI) in individuals with underlying CAD.

Background Chromosome 9p21 variants have been robustly associated with coronary heart disease, but questions remain on the mechanism of risk, specifically whether the locus contributes to coronary atheroma burden or plaque instability.

Methods We established a collaboration of 21 studies consisting of 33,673 subjects with information on both CAD (clinical or angiographic) and MI status along with 9p21 genotype. Tabular data are provided for each cohort on the presence and burden of angiographic CAD, MI cases with underlying CAD, and the diabetic status of all subjects.

Results We first confirmed an association between 9p21 and CAD with angiographically defined cases and control subjects (pooled odds ratio [OR]: 1.31, 95% confidence interval [CI]: 1.20 to 1.43). Among subjects with angiographic CAD (n = 20,987), random-effects model identified an association with multivessel CAD, compared with those with single-vessel disease (OR: 1.10, 95% CI: 1.04 to 1.17)/copy of risk allele). Genotypic models showed an OR of 1.15, 95% CI: 1.04 to 1.26 for heterozygous carrier and OR: 1.23, 95% CI: 1.08 to 1.39 for homozygous carrier. Finally, there was no significant association between 9p21 and prevalent MI when both cases (n = 17,791) and control subjects (n = 15,882) had underlying CAD (OR: 0.99, 95% CI: 0.95 to 1.03)/risk allele.

Conclusions The 9p21 locus shows convincing association with greater burden of CAD but not with MI in the presence of underlying CAD. This adds further weight to the hypothesis that 9p21 locus primarily mediates an atherosclerotic phenotype. (J Am Coll Cardiol 2013;61:957–70) © 2013 by the American College of Cardiology Foundation

JACC Vol. 61, No. 9, 2013
March 5, 2013:957–70

Genome-wide association studies (GWAS) first identified the 9p21 locus as associating with coronary heart disease (CHD) in 2007 (1–3). A plethora of replication studies have since confirmed and validated this association in a series of different ethnic populations, making this the most robust genetic finding for CHD to date. The need for large study samples in many of these studies has led to phenotypic heterogeneity with inclusion of cases with acute or stable clinical presentations with presumed healthy control populations and varying definitions of CHD, including clinical or noninvasive diagnosis of coronary artery disease (CAD), angiographic CAD, validated myocardial infarction (MI), or a combination of these (4,5). This lack of phenotypic clarity has resulted in uncertainty about the primary phenotype mediated by the 9p21 locus, specifically whether it predisposes to atherosclerosis or promotes a more abrupt plaque rupture or thrombotic process leading to MI. This in turn has hampered contextualization of early functional studies attempting to resolve the underlying mechanism (6).

There have been several attempts to tease apart the closely related phenotypes of CAD and MI (7–9). In the most comprehensive analysis to date, Reilly et al. (8) demonstrated that, although 11 variants had shown robust association with MI in GWAS when compared with healthy control subjects, they did not associate with MI when both cases and control subjects had underlying CAD. It was thus proposed that the primary association for these variants was likely to be with development of CAD rather than predisposition to plaque rupture or thrombosis per se. It follows then that carriers of the risk allele at the 9p21 locus should demonstrate a greater burden of coronary atherosclerosis compared with non-risk carriers. Although studies with computerized tomography have demonstrated a correlation between 9p21 and greater coronary artery calcification, indicating a role in predisposing to atheroma formation (10,11), studies using invasive coronary angiography as a more direct and widely available means of visualizing plaque have demonstrated discrepant results, leading to ongoing uncertainty with regard to the mechanism of risk (12–15).

To address this lack of consistency we sought to establish a collaboration of genetic studies and perform a comprehensive meta-analysis of the association between 9p21 and angiographically defined CAD burden as well as to replicate the lack of association with superimposed MI in subjects with underlying CAD.

Methods

Search strategy and selection criteria. We performed a systematic published data search for studies of 9p21 variation in relation to CAD/MI, published before June 2011 on MEDLINE and EMBASE, combined with cross references and manual searches. Search terms included "coronary artery disease," "myocardial infarction," or "atherosclerosis," in combination with "9p21." No language restrictions were used. A hand-search of articles and cited reference search were also performed to identify all articles that cited the index publication. Experts contributed to identification of cohorts with published and unpublished data (M.R./N.J.S.). For each included cohort, data were tabulated for angiographic presence or absence of CAD, burden of CAD, number of MI cases in subjects with underlying CAD, and the diabetic status of all subjects. Published data search, data collection/abstraction, and entry were performed independently and reconciled by 2 trained investigators (K.C. and R.P.).

From the *William Harvey Research Institute, Barts and the London School of Medicine and Dentistry, Queen Mary University London, London, United Kingdom; †Department of Medicine, Cardiff University, Cardiff, United Kingdom; ‡Department of Medicine, Emory University School of Medicine, Atlanta, Georgia; §MRC biostatistics unit, Cambridge, United Kingdom; ‖Leicester National Institute for Health Research Biomedical Research Unit in Cardiovascular Disease, Glenfield Hospital, Leicester, United Kingdom; ¶Cardiovascular Institute, the Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania; #Cardiovascular Research Institute, MedStar Health Research Institute, Washington Hospital Center, Washington DC; **Department of Epidemiology, Emory University Rollins School of Public Health, Atlanta, Georgia; ††Center for Human Genetics, Department of Medicine, Duke University, Durham, North Carolina; ‡‡Intermountain Heart Institute, Intermountain Medical Center, Salt Lake City, Utah; §§Department of Preventive Medicine, Institute for Genetic Medicine, Keck School of Medicine, University of Southern California, Los Angeles, California; ‖‖Department of Molecular Pathogenesis, Medical Research Institute, Tokyo Medical and Dental University, Tokyo, Japan; ¶¶Division of Cardiology, Samsung Medical Center, Sung Kyun Kwan University School of Medicine, Seoul, Korea; ##German Heart Centre Munich, Munich, Germany; ***Christchurch Cardioendocrine Research Group, Department of Medicine, University of Otago, Christchurch, New Zealand; †††Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, United Kingdom; ‡‡‡Institute of Clinical Molecular Biology, Christian-Albrechts-University, Kiel, Germany; §§§Klinik für Innere Medizin, Kreiskrankenhaus Rendsburg, Rendsburg, Germany; ‖‖‖Department of Medicine, Stanford University of Medicine, Stanford, California; ¶¶¶Division of Research, Kaiser Permanente, Oakland, California; ###Department of Molecular Cardiology, Center for Cardiovascular Genetics, Department of Cardiovascular Medicine, Cleveland Clinic, Cleveland, Ohio; ****University of Florida, Health Science Center, Gainesville, Florida; ††††London School of Hygiene and Tropical Medicine, London, United Kingdom; ‡‡‡‡The Center for Cardiovascular Diagnostics and Prevention, Cleveland Clinic, Cleveland, Ohio; Section for Epidemiology, Institute for Experimental Medicine, Christian-Albrechts-University of Kiel, and PopGen Biobank, University Hospital Schleswig-Holstein, Kiel, Germany; §§§§Department of Cardiovascular Medicine, University of Oxford, Oxford, United Kingdom; ¶¶¶¶Vorarlberg Institute for Vascular Investigation and Treatment (VIVIT), Feldkirch, Austria; ####Department of Cardiology, Rui Jin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China; and the *****Wessex Regional Cardiac Unit, Southampton University Hospital, Southampton, United Kingdom. Dr. Newcombe was full-time employee at GlaxoSmithKline while contributing to this paper. Dr. Whittaker is an employee of and owns shares in GlaxoSmithKline. Dr. Tang reports having received research grant support from Abbott Laboratories and has served as consultants for Medtronic, Inc., and St. Jude Medical. Dr. Johnson has received grant funding from the National Institutes of Health. Dr. Wang has served as a consultant for Merck and some of his research is supported by Merck. Dr. Farrall reports that AstraZeneca provided funding for the PROCARDIS patient collection. Dr. S. Hazen reports being named as co-inventor on pending and issued patents held by the Cleveland Clinic relating to cardiovascular diagnostics; having been paid as a consultant by Cleveland Heart Lab, Esperion, Liposciences, Merck, and Pfizer; having received research funds from Abbott, Cleveland Heart Lab, Esperion and Liposciences, Inc.; and having the right to receive royalty payments for inventions or discoveries related to cardiovascular diagnostics from Abbott Laboratories, Cleveland Heart Lab, Frantz Biomarkers, Liposciences, and Siemens. For further support information, please see the end of this paper. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Drs. Chan and Patel contributed equally to this work.

Manuscript received October 4, 2012, accepted October 30, 2012.