Supplement Material

Clinical and Genetic Association of Serum Paraoxonase and Arylesterase Activities with Cardiovascular Risk

W. H. Wilson Tang, MD^{1,2}, Jaana Hartiala, MS³, Yiying Fan PhD⁴, Yuping Wu, PhD⁴,

Alexandre F.R. Stewart PhD⁵, Jeanette Erdmann PhD⁶, Sekar Kathiresan MD⁷, The

CARDIoGRAM Consortium⁸, Robert Roberts MD⁵, Ruth McPherson MD PhD⁵,

Hooman Allayee PhD³, and Stanley L. Hazen, MD PhD.^{1,2}

¹Center for Cardiovascular Diagnostics & Prevention, Department of Cell Biology, Lerner Research Institute, and ²Department of Cardiovascular Medicine, Heart and Vascular Institute, Cleveland Clinic, Cleveland, OH.

³Department of Preventive Medicine and Institute for Genetic Medicine, University of Southern California Keck School of Medicine, Los Angeles, CA.

⁴Department of Mathematics, Cleveland State University, Cleveland OH.

- ⁵John and Jennifer Ruddy Canadian Cardiovascular Genetics Centre, University of Ottawa Heart Institute, Ottawa, Canada.
- ⁶ Medizinische Klinik II, Universität zu Lübeck, 23538 Lübeck, Germany.
- ⁷Center for Human Genetic Research, Massachusetts General Hospital, Boston MA.

⁸A full list of authors and affiliations for the CARDIoGRAM Consortium is provided in the supplemental data.

Address for Correspondence: E-mail: hazens@ccf.org

	Serum Paraoxonase Activity				Serum Arylesterase Activity			
SNP	p-value ^a	p-value ^b	p-value ^c	p-value ^d	p-value ^a	p-value ^b	p-value ^c	p-value ^d
rs2269829	3.27×10^{-288}	4.02×10^{-288}	2.83 x10 ⁻²⁸⁸	3.49 x10 ⁻²⁸⁸	4.22×10^{-11}	3.54x10 ⁻¹¹	3.96x10 ⁻¹¹	3.33x10 ⁻¹¹
rs662 (Q192R)	3.31x10 ⁻²⁹⁵	4.36 x10 ⁻²⁹⁵	2.43 x10 ⁻²⁹⁵	3.20 x10 ⁻²⁹⁵	9.43x10 ⁻¹¹	8.19x10 ⁻¹¹	8.63 x10 ⁻¹¹	7.50 x10 ⁻¹¹
rs2057681	1.18×10^{-303}	1.56 x10 ⁻³⁰³	9.92 x10 ⁻³⁰⁴	$1.32 \text{ x} 10^{-303}$	2.11x10 ⁻¹⁰	1.83 x10 ⁻¹⁰	1.98 x10 ⁻¹⁰	1.71 x10 ⁻¹⁰
rs854560 (L55M)	$1.27 \mathrm{x} 10^{-140}$	$1.22 \text{ x} 10^{-140}$	$1.31 \text{ x} 10^{-140}$	$1.26 \text{ x} 10^{-140}$	2.03×10^{-38}	2.48 x10 ⁻³⁸	2.14 x10 ⁻³⁸	2.61 x10 ⁻³⁸
rs854570	2.90x10 ⁻⁰⁹	2.87 x10 ⁻⁰⁹	$3.00 \text{ x}10^{-09}$	2.97 x10 ⁻⁰⁹	5.10×10^{-106}	4.98 x10 ⁻¹⁰⁶	$3.12 \text{ x} 10^{-106}$	3.07 x10 ⁻¹⁰⁶
rs854572	1.23×10^{-35}	1.18 x10 ⁻³⁵	$1.32 \text{ x} 10^{-35}$	1.27 x10 ⁻³⁵	4.99x10 ⁻¹¹⁶	7.21 x10 ⁻¹¹⁶	3.73 x10 ⁻¹¹⁶	5.42 x10 ⁻¹¹⁶
rs705382	2.92x10 ⁻⁰⁹	2.90 x10 ⁻⁰⁹	3.03 x10 ⁻⁰⁹	3.00 x10 ⁻⁰⁹	1.98x10 ⁻¹⁰⁶	1.92 x10 ⁻¹⁰⁶	1.15 x10 ⁻¹⁰⁶	1.12 x10 ⁻¹⁰⁶
rs757158	3.97x10 ⁻³⁸	3.87 x10 ⁻³⁸	4.28 x10 ⁻³⁸	4.17 x10 ⁻³⁸	$1.04 \mathrm{x} 10^{-104}$	1.28 x10 ⁻¹⁰⁴	8.10 x10 ⁻¹⁰⁵	1.00 x10 ⁻¹⁰⁴

Supplemental Table I Association of Lead SNPs on Chromosome 7 with Adjustment for BMI and Statin Use.

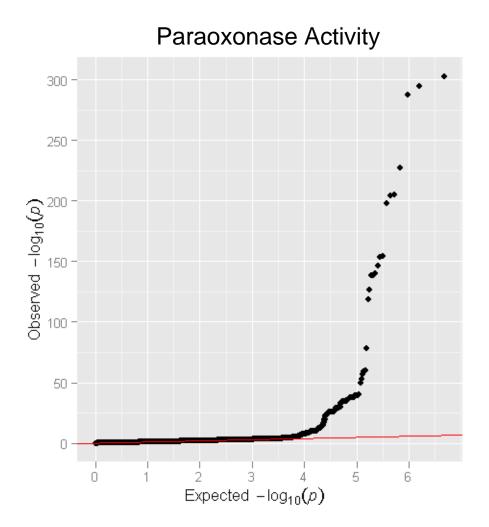
^ap-values obtained with adjustment for age and gender. ^bp-values obtained with adjustment for age, gender, and BMI.

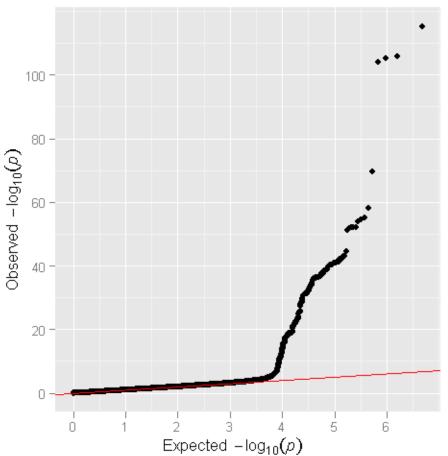
^cp-values obtained with adjustment for age gender, and statin use. ^dp-values obtained with adjustment for age, gender, BMI, and statin use.

SNP	Total Cholesterol	LDL cholesterol	HDL cholesterol	^b C-reactive Protein	Creatinine clearance
rs2269829	0.12	0.12	0.77	0.29	0.19
rs662 (Q192R)	0.13	0.11	0.76	0.31	0.28
rs2057681	0.13	0.12	0.92	0.35	0.30
rs854560 (L55M)	0.76	0.54	0.40	0.49	0.15
rs854570	0.58	0.17	0.57	0.31	0.87
rs854572	0.83	0.33	0.52	0.70	0.82
rs705382	0.57	0.17	0.55	0.32	0.86
rs757158	0.94	0.43	0.78	0.68	0.88

Supplemental Table II Association of Identified SNPs with CAD Biomarkers.

^ap-values are shown for association of lead SNPs on chromosome 7 with CAD biomarkers, with adjustment for age and gender. ^blog-transformed prior to analysis. Supplemental Figure I Q-Q plots for GWAS of paraoxonase and arylesterase activity.





Arylesterase Activity

Supplement: The CARDIoGRAM Consortium

Executive Committee: Sekar Kathiresan^{1,2,3}, Muredach P. Reilly⁴, Nilesh J. Samani^{5,6}, Heribert Schunkert^{7,79}

Executive Secretary: Jeanette Erdmann^{7,79}

Steering Committee: Themistocles L. Assimes⁸, Eric Boerwinkle⁹, Jeanette Erdmann^{7,79} Alistair Hall¹⁰, Christian Hengstenberg¹¹, Sekar Kathiresan^{1,2,3}, Inke R. König¹², Reijo Laaksonen¹³, Ruth McPherson¹⁴, Muredach P. Reilly⁴, Nilesh J. Samani^{5,6}, Heribert Schunkert^{7,79}, John R.

Thompson¹⁵, Unnur Thorsteinsdottir^{16,17}, Andreas Ziegler¹²

Statisticians: Inke R. König¹² (chair), John R. Thompson¹⁵ (chair), Devin Absher¹⁸, Li Chen¹⁹, L.

Adrienne Cupples^{20,21}, Eran Halperin²², Mingyao Li²³, Kiran Musunuru^{1,2,3}, Michael Preuss^{12,7},

Arne Schillert¹², Gudmar Thorleifsson¹⁶, Benjamin F. Voight^{2,3,24}, George A. Wells²⁵

Writing group: Themistocles L. Assimes⁸, Panos Deloukas²⁶, Jeanette Erdmann^{7,79}, Hilma

Holm¹⁶, Sekar Kathiresan^{1,2,3}, Inke R. König¹², Ruth McPherson¹⁴, Muredach P. Reilly⁴, Robert Roberts¹⁴, Nilesh J. Samani^{5,6}, Heribert Schunkert^{7,79}, Alexandre F. R. Stewart¹⁴

ADVANCE: Devin Absher¹⁸, Themistocles L. Assimes⁸, Stephen Fortmann⁸, Alan Go²⁷, Mark Hlatky⁸, Carlos Iribarren²⁷, Joshua Knowles⁸, Richard Myers¹⁸, Thomas Quertermous⁸, Steven Sidney²⁷, Neil Risch²⁸, Hua Tang²⁹

CADomics: Stefan Blankenberg³⁰, Tanja Zeller³⁰, Arne Schillert¹², Philipp Wild³⁰, Andreas Ziegler¹², Renate Schnabel³⁰, Christoph Sinning³⁰, Karl Lackner³¹, Laurence Tiret³², Viviane Nicaud³², Francois Cambien³², Christoph Bickel³⁰, Hans J. Rupprecht³⁰, Claire Perret³², Carole Proust³², Thomas Münzel³⁰

CHARGE: Maja Barbalic³³, Joshua Bis³⁴, Eric Boerwinkle⁹, Ida Yii-Der Chen³⁵, L. Adrienne Cupples^{20,21}, Abbas Dehghan³⁶, Serkalem Demissie-Banjaw^{37,21}, Aaron Folsom³⁸, Nicole Glazer³⁹, Vilmundur Gudnason^{40,41}, Tamara Harris⁴², Susan Heckbert⁴³, Daniel Levy²¹, Thomas Lumley⁴⁴, Kristin Marciante⁴⁵, Alanna Morrison⁴⁶, Christopher J. O'Donnell⁴⁷, Bruce M. Psaty⁴⁸, Kenneth Rice⁴⁹, Jerome I. Rotter³⁵, David S. Siscovick⁵⁰, Nicholas Smith⁴³, Albert Smith^{40,41}, Kent D. Taylor³⁵, Cornelia van Duijn³⁶, Kelly Volcik⁴⁶, Jaqueline Whitteman³⁶, Vasan Ramachandran⁵¹, Albert Hofman³⁶, Andre Uitterlinden^{52,36}

deCODE: Solveig Gretarsdottir¹⁶, Jeffrey R. Gulcher¹⁶, Hilma Holm¹⁶, Augustine Kong¹⁶, Kari Stefansson^{16,17}, Gudmundur Thorgeirsson^{53,17}, Karl Andersen^{53,17}, Gudmar Thorleifsson¹⁶, Unnur Thorsteinsdottir^{16,17}

GERMIFS I and II: Jeanette Erdmann^{7,79}, Marcus Fischer¹¹, Anika Grosshennig^{12,7}, Christian Hengstenberg¹¹, Inke R. König¹², Wolfgang Lieb⁵⁴, Patrick Linsel-Nitschke⁷, Michael Preuss^{12,7}, Klaus Stark¹¹, Stefan Schreiber⁵⁵, H.-Erich Wichmann^{56,58,59}, Andreas Ziegler¹², Heribert Schunkert^{7,79}

GERMIFS III (**KORA**): Zouhair Aherrahrou^{7,79}, Petra Bruse^{7,79}, Angela Doering⁵⁶, Jeanette Erdmann^{7,79}, Christian Hengstenberg¹¹, Thomas Illig⁵⁶, Norman Klopp⁵⁶, Inke R. König¹², Patrick Diemert⁷, Christina Loley^{12,7}, Anja Medack^{7,79}, Christina Meisinger⁵⁶, Thomas Meitinger^{57,60}, Janja Nahrstedt^{12,7}, Annette Peters⁵⁶, Michael Preuss^{12,7}, Klaus Stark¹¹, Arnika K. Wagner⁷, H.-Erich Wichmann^{56,58,59}, Christina Willenborg^{,7,79}, Andreas Ziegler¹², Heribert Schunkert^{7,79}

LURIC/AtheroRemo: Bernhard O. Böhm⁶¹, Harald Dobnig⁶², Tanja B. Grammer⁶³, Eran Halperin²², Michael M. Hoffmann⁶⁴, Marcus Kleber⁶⁵, Reijo Laaksonen¹³, Winfried März^{63,66,67}, Andreas Meinitzer⁶⁶, Bernhard R. Winkelmann⁶⁸, Stefan Pilz⁶², Wilfried Renner⁶⁶, Hubert Scharnagl⁶⁶, Tatjana Stojakovic⁶⁶, Andreas Tomaschitz⁶², Karl Winkler⁶⁴ **MIGen**: Benjamin F. Voight^{2,3,24}, Kiran Musunuru^{1,2,3}, Candace Guiducci³, Noel Burtt³, Stacey B. Gabriel³, David S. Siscovick⁵⁰, Christopher J. O'Donnell⁴⁷, Roberto Elosua⁶⁹, Leena Peltonen⁴⁹, Veikko Salomaa⁷⁰, Stephen M. Schwartz⁵⁰, Olle Melander²⁶, David Altshuler^{71,3}, Sekar Kathiresan^{1,2,3}

OHGS: Alexandre F. R. Stewart¹⁴, Li Chen¹⁹, Sonny Dandona¹⁴, George A. Wells²⁵, Olga Jarinova¹⁴, Ruth McPherson¹⁴, Robert Roberts¹⁴

PennCATH/MedStar: Muredach P. Reilly⁴, Mingyao Li²³, Liming Qu²³, Robert Wilensky⁴, William Matthai⁴, Hakon H. Hakonarson⁷², Joe Devaney⁷³, Mary Susan Burnett⁷³, Augusto D. Pichard⁷³, Kenneth M. Kent⁷³, Lowell Satler⁷³, Joseph M. Lindsay⁷³, Ron Waksman⁷³, Christopher W. Knouff⁷⁴, Dawn M. Waterworth⁷⁴, Max C. Walker⁷⁴, Vincent Mooser⁷⁴, Stephen E. Epstein⁷³, Daniel J. Rader^{75,4}

WTCCC: Nilesh J. Samani^{5,6}, John R. Thompson¹⁵, Peter S. Braund⁵, Christopher P. Nelson⁵, Benjamin J. Wright⁷⁶, Anthony J. Balmforth⁷⁷, Stephen G. Ball⁷⁸, Alistair S. Hall¹⁰, Wellcome Trust Case Control Consortium

Affiliations

1 Cardiovascular Research Center and Cardiology Division, Massachusetts General Hospital, Boston, MA, USA; 2 Center for Human Genetic Research, Massachusetts General Hospital, Boston, MA, USA; 3 Program in Medical and Population Genetics, Broad Institute of Harvard and Massachusetts Institute of Technology (MIT), Cambridge, MA, USA; 4 The Cardiovascular Institute, University of Pennsylvania, Philadelphia, PA, USA; 5 Department of Cardiovascular Sciences, University of Leicester, Glenfield Hospital, Leicester, UK; 6 Leicester National Institute for Health Research Biomedical Research Unit in Cardiovascular Disease, Glenfield Hospital, Leicester, LE3 9QP, UK; 7 Medizinische Klinik II, Universität zu Lübeck, Lübeck, Germany; 8 Department of Medicine, Stanford University School of Medicine, Stanford, CA, USA; 9 University of Texas Health Science Center, Human Genetics Center and Institute of Molecular Medicine, Houston, TX, USA; 10 Division of Cardiovascular and Neuronal Remodelling, Multidisciplinary Cardiovascular Research Centre, Leeds Institute of Genetics, Health and Therapeutics, University of Leeds, UK; 11 Klinik und Poliklinik für Innere Medizin II, Universität Regensburg, Regensburg, Germany; 12 Institut für Medizinische Biometrie und Statistik, Universität zu Lübeck, Lübeck, Germany; 13 Science Center, Tampere University Hospital, Tampere, Finland; 14 The John & Jennifer Ruddy Canadian Cardiovascular Genetics Centre, University of Ottawa Heart Institute, Ottawa, Canada; 15 Department of Health Sciences, University of Leicester, Leicester, UK; 16 deCODE Genetics, 101 Reykjavik, Iceland; 17 University of Iceland, Faculty of Medicine, 101 Reykjavik, Iceland; 18 Hudson Alpha Institute, Huntsville, Alabama, USA; 19 Cardiovascular Research Methods Centre, University of Ottawa Heart Institute, 40 Ruskin Street, Ottawa, Ontario, Canada, K1Y 4W7; 20 Department of Biostatistics, Boston University School of Public Health, Boston, MA USA; 21 National Heart, Lung and Blood Institute's Framingham Heart Study, Framingham, MA, USA; 22 The Blavatnik School of Computer Science and the Department of Molecular Microbiology and Biotechnology, Tel-Aviv University, Tel-Aviv, Israel, and the International Computer Science Institute, Berkeley, CA, USA; 23 Biostatistics and Epidemiology, University of Pennsylvania, Philadelphia, PA, USA; 24 Department of Medicine, Harvard Medical School, Boston, MA, USA; 25 Research Methods, Univ Ottawa Heart Inst; 26 Department of Clinical Sciences, Hypertension and Cardiovascular Diseases, Scania University Hospital, Lund University, Malmö, Sweden; 27 Division of Research, Kaiser Permanente, Oakland, CA, USA; 28 Institute

for Human Genetics, University of California, San Francisco, San Francisco, CA, USA; 29 Dept Cardiovascular Medicine, Cleveland Clinic; 30 Medizinische Klinik und Poliklinik, Johannes-Gutenberg Universität Mainz, Universitätsmedizin, Mainz, Germany; 31 Institut für Klinische Chemie und Laboratoriumsmediizin, Johannes-Gutenberg Universität Mainz, Universitätsmedizin, Mainz, Germany; 32 INSERM UMRS 937, Pierre and Marie Curie University (UPMC, Paris 6) and Medical School, Paris, France; 33 University of Texas Health Science Center, Human Genetics Center, Houston, TX, USA; 34 Cardiovascular Health Resarch Unit and Department of Medicine, University of Washington, Seattle, WA USA; 35 Cedars-Sinai Medical Center, Medical Genetics Institute, Los Angeles, CA, USA; 36 Erasmus Medical Center, Department of Epidemiology, Rotterdam, The Netherlands; 37 Boston University, School of Public Health, Boston, MA, USA; 38 University of Minnesota School of Public Health, Division of Epidemiology and Community Health, School of Public Health (A.R.F.), Minneapolis, MN, USA; 39 University of Washington, Cardiovascular Health Research Unit and Department of Medicine, Seattle, WA, USA; 40 Icelandic Heart Association, Kopavogur Iceland; 41 University of Iceland, Reykjavik, Iceland; 42 Laboratory of Epidemiology, Demography, and Biometry, Intramural Research Program, National Institute on Aging, National Institutes of Health, Bethesda MD, USA; 43 University of Washington, Department of Epidemiology, Seattle, WA, USA; 44 University of Washington, Department of Biostatistics, Seattle, WA, USA; 45 University of Washington, Department of Internal Medicine, Seattle, WA, USA; 46 University of Texas, School of Public Health, Houston, TX, USA; 47 National Heart, Lung and Blood Institute, Framingham Heart Study, Framingham, MA and Cardiology Division, Massachusetts General Hospital, Boston, MA, USA; 48 Center for Health Studies, Group Health, Departments of Medicine, Epidemiology, and Health Services, Seattle, WA, USA; 49 The

Wellcome Trust Sanger Institute, The Wellcome Trust Genome Campus, Hinxton, Cambridge, UK; 50 Cardiovascular Health Research Unit, Departments of Medicine and Epidemiology, University of Washington, Seattle; 51 Boston University Medical Center, Boston, MA, USA; 52 Department of Internal Medicine, Erasmus Medical Center, Rotterdam, The Netherlands; 53 Department of Medicine, Landspitali University Hospital, 101 Reykjavik, Iceland; 54 Boston University School of Medicine, Framingham Heart Study, Framingham, MA, USA; 55 Institut für Klinische Molekularbiologie, Christian-Albrechts Universität, Kiel, Germany; 56 Institute of Epidemiology, Helmholtz Zentrum München – German Research Center for Environmental Health, Neuherberg, Germany; 57 Institut für Humangenetik, Helmholtz Zentrum München, Deutsches Forschungszentrum für Umwelt und Gesundheit, Neuherberg, Germany; 58 Institute of Medical Information Science, Biometry and Epidemiology, Ludwig-Maximilians-Universität München, Germany; 59 Klinikum Grosshadern, Munich, Germany; 60 Institut für Humangenetik, Technische Universität München, Germany; 61 Division of Endocrinology and Diabetes, Graduate School of Molecular Endocrinology and Diabetes, University of Ulm, Ulm, Germany; 62 Division of Endocrinology, Department of Medicine, Medical University of Graz, Austria; 63 Synlab Center of Laboratory Diagnostics Heidelberg, Heidelberg, Germany; 64 Division of Clinical Chemistry, Department of Medicine, Albert Ludwigs University, Freiburg, Germany; 65 LURIC non profit LLC, Freiburg, Germany; 66 Clinical Institute of Medical and Chemical Laboratory Diagnostics, Medical University Graz, Austria; 67 Institute of Public Health, Social and Preventive Medicine, Medical Faculty Manneim, University of Heidelberg, Germany; 68 Cardiology Group Frankfurt-Sachsenhausen, Frankfurt, Germany; 69 Cardiovascular Epidemiology and Genetics Group, Institut Municipal d'Investigació Mèdica, Barcelona; Ciber Epidemiología y Salud Pública (CIBERSP), Spain; 70 Chronic Disease

Epidemiology and Prevention Unit, Department of Chronic Disease Prevention, National Institute for Health and Welfare, Helsinki, Finland; 71 Department of Molecular Biology and Center for Human Genetic Research, Massachusetts General Hospital, Harvard Medical School, Boston, USA; 72 The Center for Applied Genomics, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA; 73 Cardiovascular Research Institute, Medstar Health Research Institute, Washington Hospital Center, Washington, DC 20010, USA; 74 Genetics Division and Drug Discovery, GlaxoSmithKline, King of Prussia, Pennsylvania 19406, USA; 75 The Institute for Translational Medicine and Therapeutics, School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; 76 Department of Cardiovascular Surgery, University of Leicester, Leicester, UK; 77 Division of Cardiovascular and Diabetes Research, Multidisciplinary Cardiovascular Research Centre, Leeds Institute of Genetics, Health and Therapeutics, University of Leeds, Leeds, LS2 9JT, UK; 78 LIGHT Research Institute, Faculty of Medicine and Health, University of Leeds, Leeds, UK; 79 Deutsches Zentrum für Herz-Kreislauf-Forschung (DZHK), Universität zu Lübeck, Lübeck, Germany

Sources of Funding

The **ADVANCE** study was supported by a grant from the Reynold's Foundation and NHLBI grant HL087647.

Genetic analyses of **CADomics** were supported by a research grant from Boehringer Ingelheim. Recruitment and analysis of the CADomics cohort was supported by grants from Boehringer Ingelheim and PHILIPS medical Systems, by the Government of Rheinland-Pfalz in the context of the "Stiftung Rheinland-Pfalz für Innovation", the research program "Wissen schafft Zukunft" and by the Johannes-Gutenberg University of Mainz in the context of the "Schwerpunkt Vaskuläre Prävention" and the "MAIFOR grant 2001", by grants from the Fondation de France, the French Ministry of Research, and the Institut National de la Santé et de la Recherche Médicale.

The **deCODE** CAD/MI Study was sponsored by NIH grant, National Heart, Lung and Blood Institute R01HL089650-02.

The German MI Family Studies (**GerMIFS I-III** (**KORA**)) were supported by the Deutsche Forschungsgemeinschaft and the German Federal Ministry of Education and Research (BMBF) in the context of the German National Genome Research Network (NGFN-2 and NGFN-plus), the EU funded integrated project Cardiogenics (LSHM-CT-2006-037593) and ENGAGE, and the bi-national BMBF/ANR funded project CARDomics (01KU0908A).

LURIC has received funding from the EU framework 6 funded Integrated Project "Bloodomics" (LSHM-CT-2004-503485), the EU framework 7 funded Integrated Project AtheroRemo (HEALTH-F2-2008-201668) and from Sanofi/Aventis, Roche, Dade Behring/Siemens, and AstraZeneca.

The **MIGen** study was funded by the US National Institutes of Health (NIH) and National Heart, Lung, and Blood Institute's STAMPEED genomics research program through R01 HL087676. Ron Do from the MIGen study is supported by a Canada Graduate Doctoral Scholarship from the Canadian Institutes of Health Research.

Recruitment of **PennCATH** was supported by the Cardiovascular Institute of the University of Pennsylvania. Recruitment of the **MedStar** sample was supported in part by the MedStar Research Institute and the Washington Hospital Center and a research grant from GlaxoSmithKline. Genotyping of PennCATH and Medstar was performed at the Center for Applied Genomics at the Children's Hospital of Philadelphia and supported by GlaxoSmithKline through an Alternate Drug Discovery Initiative research alliance award (M. P. R. and D. J. R.) with the University of Pennsylvania School of Medicine. The **Ottawa Heart Genomic Study** was supported by CIHR #MOP--82810 (R. R.), CFI #11966 (R. R.), HSFO #NA6001 (R. McP.), CIHR #MOP172605 (R. McP.), CIHR #MOP77682 (A. F. R. S.).

The **WTCCC** Study was funded by the Wellcome Trust. Recruitment of cases for the WTCCC Study was carried out by the British Heart Foundation (BHF) Family Heart Study Research Group and supported by the BHF and the UK Medical Research Council. N. J. S. and S. G. B. hold chairs funded by the British Heart Foundation. N. J. S. and A.H.G are also supported by the Leicester NIHR Biomedical Research Unit in Cardiovascular Disease and the work described in this paper is part of the research portfolio of the Leicester NIHR Biomedical Research Unit.

The **Age, Gene/Environment Susceptibility Reykjavik Study** has been funded by NIH contract N01-AG-12100, the NIA Intramural Research Program, Hjartavernd (the Icelandic Heart Association), and the Althingi (the Icelandic Parliament).

The **Cleveland Clinic GeneBank** study was supported by NIH grants P01 HL098055, P01HL076491-06, R01DK080732, P01HL087018, and 1RO1HL103931-01.

The collection of clinical and sociodemographic data in the **Dortmund Health Study** was supported by the German Migraine- & Headache Society (DMKG) and by unrestricted grants of equal share from Astra Zeneca, Berlin Chemie, Boots Healthcare, Glaxo-Smith-Kline, McNeil Pharma (former Woelm Pharma), MSD Sharp & Dohme and Pfizer to the University of Muenster. Blood collection was done through funds from the Institute of Epidemiology and Social Medicine, University of Muenster.

The **EPIC-Norfolk study** is supported by the Medical Research Council UK and Cancer Research UK.

The **EpiDREAM study** is supported by the Canadian Institutes fo Health Research, Heart and Stroke Foundation of Ontario, Sanofi-Aventis, GlaxoSmithKline and King Pharmaceuticals.

Funding for Andrew Lotery from the **LEEDS** study was provided by tha T.F.C. Frost charity and the Macular Disease Society.

The **Rotterdam Study** is supported by the Erasmus Medical Center and Erasmus University Rotterdam; the Netherlands Organization for Scientific Research; the Netherlands Organization for Health Research and Development (ZonMw); the Research Institute for Diseases in the Elderly; The Netherlands Heart Foundation; the Ministry of Education, Culture and Science; the Ministry of Health Welfare and Sports; the European Commission (DG XII); and the Municipality of Rotterdam. Support for genotyping was provided by the Netherlands Organization for Scientific Research (NWO) (175.010.2005.011, 911.03.012), the Netherlands Genomics Initiative (NGI)/ NWO project nr. 050-060-810 and Research Institute for Diseases in the Elderly (RIDE). Abbas Dehghan is supported by a grant from NWO (Vici, 918-76-619).

The SAS study was funded by the British Heart Foundation.

The Swedish Research Council, the Swedish Heart & Lung Foundation and the Stockholm Council (ALF) supported the **SHEEP** study.

SMILE was funded by the Netherlands Heart foundation (NHS 92345). Dr Rosendaal is a recipient of the Spinoza Award of the Netherlands Organisation for Scientific Research (NWO) which was used for part of this work.

The **Verona Heart Study** was funded by grants from the Italian Ministry of University and Research, the Veneto Region, and the Cariverona Foundation, Verona.

The **Atherosclerosis Risk in Communities Study** is carried out as a collaborative study supported by National Heart, Lung, and Blood Institute contracts N01-HC-55015, N01-HC-55016, N01-HC-55018, N01-HC-55019, N01-HC-55020, N01-HC-55021, and N01-HC-55022. The authors thank the staff and participants of the ARIC study for their important contributions.

The **KORA** (Kooperative Gesundheitsforschung in der Region Augsburg) research platform was initiated and financed by the Helmholtz Zentrum München - National Research Center for Environmental Health, which is funded by the German Federal Ministry of Education, Science, Research and Technology and by the State of Bavaria. Part of this work was financed by the German National Genome Research Network (NGFN-2 and NGFNPlus) and within the Munich Center of Health Sciences (MC Health) as part of LMUinnovativ.