Supplemental Materials

Genome-wide Analysis Identifies Novel Susceptibility Loci for Myocardial Infarction

Hartiala, Han, et al.

Address correspondence and reprint requests to:

Hooman Allayee, PhD
Department of Preventive Medicine
Keck School of Medicine of USC 2250
Alcazar Street, CSC202
Los Angeles, CA 90033 Phone:
(323) 442-1736
Fax: (332) 442-2764
Email: hallayee@usc.edu

Detailed Description of Cohorts Used for MI Replication Analyses

Cleveland Clinic GeneBank: The Cleveland Clinic GeneBank cohort is a single site sample repository generated from ~10,000 consecutive patients undergoing elective diagnostic coronary angiography or elective cardiac computed tomographic angiography with extensive clinical and laboratory characterization and longitudinal observation. The present analysis included 3,484 subjects of northern European ancestry from the GeneBank cohort, all of whom had coronary artery disease (CAD) has defined by angiographic evidence of ≥50% stenosis in one or more major epicardial vessel and/or a documented history of known CAD. Among these 3,395 subjects, 1,827 had an adjudicated prior diagnosis of myocardial infarction (MI) based on defined electrocardiographic changes or elevated cardiac enzymes, with the remaining 1,568 subjects having CAD but no history of MI. Subject recruitment occurred between 2001 and 2007. Ethnicity was self-reported and information regarding demographics, medical history, and medication use was obtained by patient interviews and confirmed by chart reviews. All clinical outcome data were verified by source documentation. The GeneBank cohort has been used previously for discovery and replication of novel genes and risk factors for atherosclerotic disease[1-5].

Emory Cardiovascular Biobank: The Emory Cardiovascular Biobank is a prospective cohort of 5,876 patients undergoing elective or emergent heart catheterization for suspected or confirmed CAD at three Emory healthcare sites in Atlanta, GA. Subjects with congenital heart disease and heart transplantation cancer were excluded. Replication analyses were carried out using genotypes or imputed genotypes obtained from the Illumina Infinium Multi-Ethnic Global Array. The study was approved by the Institutional Review Board of Emory University, Atlanta,

GA. All subjects provided written informed consent at the time of enrollment.

ANGES/FINCAVAS: The Angiography and Genes Study (ANGES) cohort consists of 1,000 Finnish individuals who underwent coronary angiography at Tampere University Hospital to detect CAD between September 2002 and July 2005. Data were collected on age, sex, body mass index, alcohol consumption, smoking, medication as well as traditional risk factors of atherosclerosis. A clinical diagnosis of MI was based on symptoms, electrocardiographic findings and biochemical marker tests measuring troponin I and creatine kinase. Previous cardiovascular diseases, therapeutic procedures and data on CAD and MI were retrieved from patient records at Tampere University Hospital. Follow-up data were derived from the national health care registers maintained by the National Institute for Welfare and Health. Replication analyses in ANGES/FINCAVAS were carried out using genotypes or imputed genotypes for obtained from the Metabochip and Core Exome array. The local ethical committee has approved the study and a written informed consent was obtained from all participants[6]. The Finnish Cardiovascular Study (FINCAVAS) cohort includes 4,567 patients who underwent exercise stress tests at Tampere University Hospital. Study participants were followed up for major cardiovascular events, coronary procedures and cause of death with follow-up data gathered at 2, 5 and 10 years post-recruitment[7].

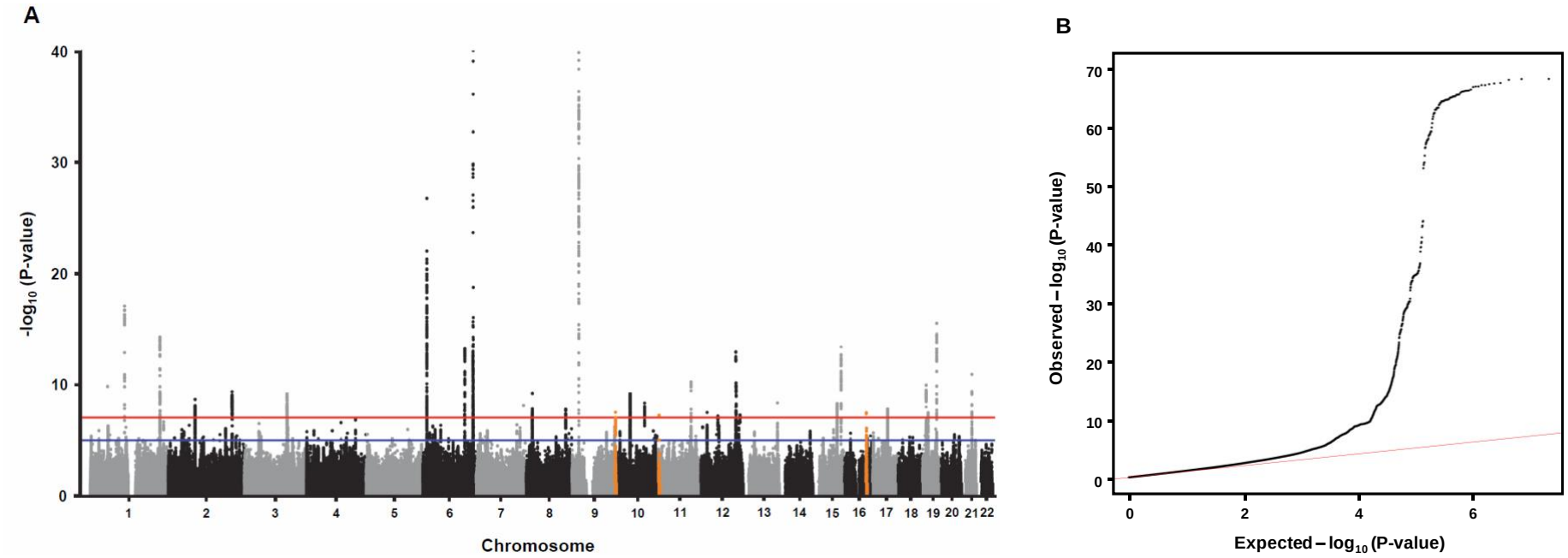
LIFE-HEART: The Leipzig Heart Study (LIFE-Heart) is an observational cohort of patients recruited at the Leipzig Heart Center, Germany. Patients with suspected CAD (CAD), stable CAD or MI were recruited. Patients received a comprehensive assessment of vessel status and cardiologic function including coronary angiography, carotid ultrasound, ankle-brachial index,

echo-cardiography and electrocardiography. Details of the study can be found in Beutner et al[8]. Replication analyses in LIFE-Heart was carried out using genotypes or imputed genotypes obtained from the Affymetrix Axiom CEU1 or Affymetrix Axiom CADLIFE arrays, as described previously by Pott et al[9]. The study was approved by the Ethics Committee of the Faculty of Medicine of Leipzig University, Germany (Reg. No 276-2005) and is registered at ClinicalTrials.gov (NCT00497887). Written informed consent was obtained from all participants included in the study.

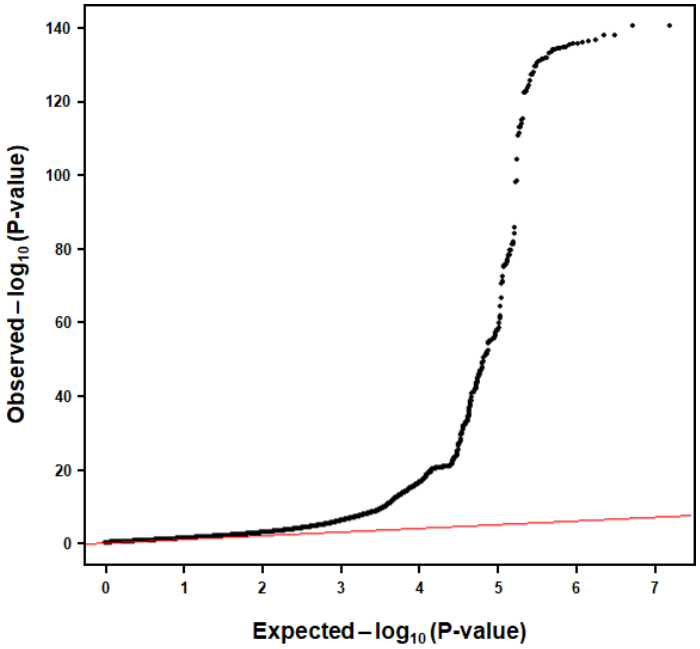
LURIC: The LUdwigshafen RIsk and Cardiovascular Health Study (LURIC) is a monocentric hospital-based prospective cohort including 3316 individuals referred for coronary angiography recruited in the Ludwigshafen Cardiac Center, southwestern Germany from 1997 – 2000[10]. Clinical indications for angiography were chest pain or a positive non-invasive stress test suggestive of myocardial ischemia. To limit clinical heterogeneity, individuals suffering from acute illnesses other than acute coronary syndrome, chronic non-cardiac diseases and a history of malignancy within the five past years were excluded. All participants completed a detailed questionnaire, which gathered information on medical history, clinical, and lifestyle factors. Fasting blood samples were obtained by venipuncture in the early morning and stored for later analyses. Information on vital status during follow-up was obtained from local registries. Death certificates, medical records of local hospitals, and autopsy data were reviewed independently by two experienced clinicians who were blinded to patient characteristics and who classified the causes of death. CAD at baseline was defined as the presence of a visible luminal narrowing (>50% stenosis) in at least one of 15 coronary segments according to the classification of the American Heart Association. Replication analyses in LURIC was carried out using genotypes or

imputed genotypes obtained from the Affymetrix 6.0 GeneChip. Study protocols were approved by the ethics committee of the "Landesärztekammer Rheinland-Pfalz" and the study was conducted in accordance with the "Declaration of Helsinki". Informed written consent was obtained from all participants.

UCORBIO: The Utrecht Coronary Biobank Study (UCORBIO) enrolled 2,591 patients who underwent coronary angiography for any indication at the University Medical Center Utrecht (UMCU). Baseline assessment and blood sampling took place between 2011 and 2014. Patients were followed up (maximum: 3 years) for the occurrence of major adverse cardiovascular events (stroke, MI, coronary revascularization, death). The study was approved by the Ethics Committee of the UMCU and was conducted according to the Declaration of Helsinki. UCORBIO is registered with clinicaltrials.gov (ID: NCT02304744).



Extended Data Figure 1. Results of GWAS analysis for MI in UK Biobank. (A) A Manhattan plot shows 1,966 significantly associated SNPs distributed among 31 loci that were significantly associated with MI in UK Biobank. Logistic regression was carried out with 10,903,881 in 454,212 controls and 17,505 MI cases, defined as positive for International Classification of Diseases version-10 (ICD10) codes: I21, I22, I23, I25.2, which include MI, and complications following acute MI. Doctor-diagnosed and self-reported MI were also included in the definition. Genome-wide thresholds for significant ($P=5.0x10^{-8}$) and suggestive ($P=5.0x10^{-6}$) association are indicated by the horizontal red and dark blue lines, respectively. P-values are truncated at -log10(P)=40. **(B)** A quantile-quantile plot shows the observed versus expected P-values from the association analyses for MI. The genomic control factor (λ) in the UK Biobank GWAS results was 1. 19 and the LD Score intercept from BOLT-LMM was 1.008 (SE=0.0074), suggesting that any inflation of test statistics was more likely due to many small genetic effects rather than population structure.



Extended Data Figure 2. Quantile-quantile plot for results of GWAS meta-analysis for MI with UK Biobank and CARDIoGRAM+C4D. The observed versus expected P-values from the fixed-effects meta-analysis for MI are shown in the quantile-quantile plot. The genomic control factor (λ) in the meta-analysis was 1.24 and the LD Score intercept was 0.969 (SE=0.0093). An LD Score intercept <1 may be due to a genomic control correction or the existence of low frequency SNPs. However, we used a linear mixed-model to control for population stratification in the UK Biobank and did not carry out a genomic control correction in the meta-analysis since the cohorts in the CARDIoGRAM+C4D Consortium were of European ancestry. Therefore, the LD Score intercept we obtained is likely as a consequence of including SNPs with MAFs as low as 0.5% in the meta-analysis. A total of ~61,000 cases and ~577,000 controls from UK Biobank (17,505 cases and 454,241 controls) and CARDIoGRAM+C4D (~44,000 cases and 123,504 controls) and 8,126,035 SNPs common to both datasets were included in the meta-analysis.

The INVENT Consortium

Philippe Amouyel[1], Mariza de Andrade[2], Saonli Basu[3], Claudine Berr[4], Jennifer A Brody[5], Daniel I Chasman[6], Jean-Francois Dartigues[7], Aaron R Folsom[8], Marine Germain[9], Hugoline de Haan[10], John Heit[11], Jeanine Houwing-Duitermaat[12], Christopher Kabrhel[13], Peter Kraft[14], Grégoire Legal[15,16], Sara Lindström[14], Ramin Monajemi[12], Pierre-Emmanuel Morange[17], Bruce M Psaty[5,18], Pieter H Reitsma[19], Paul M Ridker[20], Lynda M Rose[21], Frits R Rosendaal[10], Noémie Saut[17], Eline Slagboom[22], David Smadja[23], Nicholas L Smith[18,24,25], Pierre Suchon[17], Weihong Tang[8], Kent D Taylor[26], David-Alexandre Trégouët[9], Christophe Tzourio[27], Marieke CH de Visser[19], Astrid van Hylckama Vlieg[10], Lu-Chen Weng[8], Kerri L Wiggins[24]

INVENT Affiliations

[1] Institut Pasteur de Lille, Université de Lille Nord de France, INSERM UMR_S 744, Lille, France; Centre Hospitalier Régional Universitaire de Lille, Lille, France.

[2]Division of Biomedical Statistics and Informatics Mayo Clinic, Rochester, MN, USA.

[3]University of Minnesota, Division of Biostatistics, Minneapolis, MN, USA.

[4]INSERM Research Unit U1061 , University of Montpellier I , Montpellier, France.

[5]Cardiovascular Health Research Unit, Departments of Medicine, Epidemiology, and Health Services, University of Washington, Seattle, WA, USA.

[6]Division of Preventive Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA 02215, USA.

[7]INSERM Research Center U897, University of Bordeaux, Bordeaux, France.

[8]University of Minnesota, Division of Epidemiology and Community Health Minneapolis, MN,

USA.

[9]Institut National pour la Santé et la Recherche Médicale (INSERM), Unité Mixte de Recherche en Santé (UMR_S) 1166, F-75013, Paris, France; Sorbonne Universités, Université Pierre et Marie Curie (UPMC Univ Paris 06), UMR_S 1166, Team Genomics & Pathophysiology of Cardiovascular Diseases, F-75013, Paris, France; Institute for Cardiometabolism and Nutrition (ICAN), F-75013, Paris, France.

[10]Department of Thrombosis and Hemostasis, Leiden University Medical Center, Leiden, The Netherlands; Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, The Netherlands.

[11]Division of Cardiovascular Diseases, Mayo Clinic, Rochester, MN, USA.

[12]Department of Medical Statistics and Bioinformatics, Leiden University Medical Center, 2300 RC Leiden, Netherlands.

[13]Department of Emergency Medicine, Massachusetts General Hospital, Channing Network Medicine, Harvard Medical School, Boston, MA 2114, USA.

[14]Program in Genetic Epidemiology and Statistical Genetics, Department of Epidemiology, Harvard School of Public Health, Boston, MA 2115, USA.

[15]Université de Brest, EA3878 and CIC1412, Brest, France.

[16]Ottawa Hospital Research Institute at the University of Ottawa, Ottawa, ON, Canada.

[17]Laboratory of Haematology, La Timone Hospital, F-13385, Marseille, France; INSERM, UMR_S 1062, Nutrition Obesity and Risk of Thrombosis,F-13385, Marseille, France; Aix-Marseille University, UMR_S 1062, Nutrition Obesity and Risk of Thrombosis, F-13385, Marseille, France.

[18]Group Health Research Institute, Group Health Cooperative, Seattle WA 98101, USA.

[19]Einthoven Laboratory for Experimental Vascular Medicine, Department of Thrombosis and Hemostasis, Leiden University Medical Center, Leiden,2300 RC, Netherlands.

[20] Division of Preventive Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA 02215, USA.

[21]Division of Preventive Medicine, Brigham and Women's Hospital, Boston, MA 02215, USA.

[22]Department of Molecular Epidemiology, Leiden University Medical Center, 2300 RC Leiden, Netherlands.

[23]Université Paris Descartes, Sorbonne Paris Cité, Paris, France; AP-HP, Hopital Européen Georges Pompidou, Service d'hématologie Biologique, Paris, France; INSERM, UMR_S 1140, Faculté de Pharmacie, Paris, France.

[24]Department of Epidemiology, University of Washington, Seattle WA 98195, USA.

[25]Seattle Epidemiologic Research and Information Center, VA Office of Research and Development, Seattle WA 98108, USA.

[26]Los Angeles Biomedical Research Institute and Department of Pediatrics, Harbor-UCLA Medical Center, Torrence CA 90502, USA.

[27]INSERM Research Center U897, University of Bordeaux, Bordeaux, France.

The CHARGE Consortium Hemostasis Working Group

Nicholas L. Smith, Jennifer E. Huffman, David P. Strachan, Jie Huang, Abbas Dehghan, Stella Trompet, Lorna M. Lopez, So-Youn Shin, Jens Baumert, Veronique Vitart, Joshua C. Bis, Sarah H. Wild, Ann Rumley, Qiong Yang, Andre G Uitterlinden, David. J. Stott, Gail Davies, Angela M. Carter, Barbara Thorand, Ozren Polašek, Barbara McKnight, Harry Campbell, Alicja R. Rudnicka, Ming-Huei Chen, Brendan M. Buckley, Sarah E. Harris, Annette Peters, Drazen Pulanic, Thomas Lumley, Anton J.M. de Craen, David C. Liewald, Christian Gieger, Susan Campbell, HND, Ian Ford, Alan J. Gow, Michelle Luciano, David J. Porteous, Xiuqing Guo, Naveed Sattar, Albert Tenesa, Mary Cushman, P. Eline Slagboom, Peter M. Visscher, Tim D. Spector, Thomas Illig, Igor Rudan, Edwin G. Bovill, Alan F. Wright, Wendy L. McArdle, Geoffrey Tofler, Albert Hofman, Rudi G.J. Westendorp, John M. Starr, Peter J. Grant, Mahir Karakas, Nicholas D. Hastie, Bruce M. Psaty, James F. Wilson, DPhil, Gordon D. O. Lowe, Christopher J O'Donnell, Jacqueline CM Witteman, J. Wouter Jukema, Ian J. Deary, Nicole Soranzo, Wolfgang Koenig, Caroline Hayward.

The CHARGE Consortium Hemostasis Working Group Affiliations

Division of Community Health Sciences, St George's, University of London, UK (DPS, ARR); Division of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK (GDOL, AR); ALSPAC Laboratory, University of Bristol, UK (WLM). Departments of Epidemiology (NLS, BMP), Medicine (JCB, BMP), Biostatistics (TL, BM), Health Services (BMP), University of Washington; and Group Health Research Institute (NLS, BMP), Group Health Cooperative, Seattle, Washington, USA; Seattle Epidemiologic Research and Information

Center (NLS), Office of Research & Development, Seattle, WA, USA; Departments of Pathology (MC, EGB), Medicine (MC), University of Vermont, Burlington, Vermont USA; Medical Genetics Institute, Cedars-Sinai Medical Center, Los Angeles, California, USA (XG). MRC Human Genetics Unit, Institute of Genetics and Molecular Medicine, Western General Hospital, Edinburgh, UK (VV, SC, NDH, CH); Centre for Population Health Sciences, University of Edinburgh Medical School, Edinburgh, UK (IR); Gen Info Ltd, Zagreb, Croatia (OP, IR); Medical School, University of Zagreb, Zagreb, Croatia (OP); Division of Haematology, Department of Internal Medicine, Clinical Hospital Center Zagreb, Zagreb, Croatia, Medical School, University of Osijek, Osijek, Croatia (DP); Croatian Centre for Global Health, University of Split Medical School, Split, Croatia (IR). National Heart, Lung, and Blood Institute's Framingham Heart Study (JH, CJO) and Division of Intramural Research (C.J.O.), National Heart, Lung, and Blood Institute, Bethesda, MD; Cardiology Division (C.J.O.), Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts USA; Departments of Biostatistics (QY) and Neurology (MHC), Boston University, Boston, Massachusetts USA; Royal North Shore Hospital, University of Sydney, Australia (GT). Helmholtz Zentrum München, German Research Center for Environmental Health, Institute of Genetic Epidemiology (CG), Unit of Molecular Epidemiology (TI), Institute of Epidemiology II (JB, BT, AP), Neuherberg, Germany, Department of Internal Medicine II-Cardiology, University of Ulm Medical Center, Ulm, Germany (MK, WK). Centre for Cognitive Ageing and Cognitive Epidemiology, The University of Edinburgh, 7 George Square, Edinburgh, EH8 9JZ, UK (LML, SEH, DCL, AJG, ML, JMS, DJP, PMV, IJD); Department of Psychology, The University of Edinburgh, 7 George Square, Edinburgh, EH8 9JZ, UK (LML, GD, DCL, AJG, ML, IJD); Geriatric Medicine Unit, The University of Edinburgh, Royal

Victoria, Craigleith Road, Edinburgh, EH4 2DN, UK (JMS); Medical Genetics Section, The University of Edinburgh, Edinburgh, EH4 2XU, UK (SEH,DJP); MRC Human Genetics Unit, The Institute of Genetics and Molecular Medicine, Western General Hospital, Edinburgh, EH4 2XU, UK (AT); The Roslin Institute, Royal (Dick) School of Veterinary Studies, University of Edinburgh, Roslin, UK (AT); Queensland Statistical Genetics, Queensland Institute of Medical Research, Brisbane, Australia (PMV). MRC Human Genetics Unit, Institute of Genetics and Molecular Medicine, Western General Hospital, Edinburgh, UK (JEH, AFW); Centre for Population Health Sciences, University of Edinburgh Medical School, Edinburgh, UK (SHW, JFW, HC). Departments of Cardiology (ST, WJ), Gerontology and Geriatrics (ST, AJMdC, RGJW) and Molecular Epidemiology (PES) Leiden University Medical Center, The Netherlands; Netherlands Consortium of Healthy Ageing (PES, RGJW), The Netherlands; Division of Cardiovascular and Medical Sciences (DJS, GDOL, AR) and Robertson Center for Biostatistics (IF) University of Glasgow, Glasgow, UK; BHF Glasgow Cardiovascular Research Centre (NS), Faculty of Medicine, Glasgow, UK; Department of Pharmacology and Therapeutics, University College Cork, Ireland (BMB); Durrer Center for Cardiogenetic Research, Amsterdam, The Netherlands (WJ); Interuniversity Cardiology Institute of the Netherlands, Utrecht, The Netherlands (WJ). Department of Epidemiology (AD, AGU, AH, JCMW) and Internal Medicine (AGU), Erasmus University Medical Center, Rotterdam, The Netherlands; Netherlands Consortium for Healthy Aging (AD, AGU, AH, JCMW). Human Genetics Department (SYS, NS), Wellcome Trust Sanger Institute, Hinxton, Cambridge, UK; Department of Twin Research & Genetic Epidemiology Unit (TDS, NS), King's College London (AMC, PJG), London, UK; Division of Cardiovascular and Diabetes Research, Leeds University, Leeds, UK.

The GENIUS-CHD Consortium

Riyaz S. Patel[1,2],* Amand F. Schmidt[1,3,4],* Vinicius Tragante[3],* Raymond O. McCubrey[5], Michael V. Holmes[6,7,8], Laurence Howe[1], Kenan Direk[1], Axel Åkerblom[9,10], Karin Leander[11], Salim S. Virani[12,13], Karol A. Kaminski[14,15], Jochen D. Muehlschlegel[16,17], Marie-Pierre Dubé[31,32], Hooman Allayee[18], Peter Almgren[19], Maris Alver[20,21], Ekaterina V. Baranova[22], Hassan Behloui[23], Bram Boeckx[24,25], Peter S. Braund[26,27], Lutz P. Breitling[28], Graciela Delgado[29], Nubia E. Duarte[30], Line Dufresne[23,33], Niclas Eriksson[9], Luisa Foco[34], Crystel M. Gijsberts[35], Yan Gong[36], Jaana Hartiala[18,37], Mahyar Heydarpour[16,17], Jaroslav A. Hubacek[38], Marcus Kleber[29], Daniel Kofink[3], Pekka Kuukasjärvi[39], Vei-Vei Lee[40], Andreas Leiherer[41,42,43], Petra A. Lenzini[44], Daniel Levin[45], Leo-Pekka Lyytikäinen[46,47], Nicola Martinelli[48], Ute Mons[28], Christopher P. Nelson[26,27], Kjell Nikus[49,50], Anna P. Pilbrow[51], Rafal Ploski[52], Yan V. Sun[53,54], Michael W.T. Tanck[55], W.H.Wilson Tang[56,57], Stella Trompet[58,59], Sander W. van der Laan[35], Jessica Van Setten, Ragnar O. Vilmundarson[60,61], Chiara Viviani Anselmi[62], Efthymia Vlachopoulou[63], Eric Boerwinkle[64], Carlo Briguori[65], John F. Carlquist[5,66], Kathryn F. Carruthers[67], Gavino Casu[68], John Deanfield[1,2], Panos Deloukas[69,70], Frank Dudbridge[71], Natalie Fitzpatrick[72], Bruna Gigante[11], Stefan James[9,73], Marja-Liisa Lokki[63], Paulo A. Lotufo[74], Nicola Marziliano[68], Ify R Mordi[45], Joseph B. Muhlestein[5,66], Chris Newton Cheh[75], Jan Pitha[38], Christoph H. Saely[41,42,76], Ayman Samman-Tahhan[77], Pratik B. Sandesara[77], Andrej Teren[78,79], Adam Timmis[72,80], Frans Van de Werf[81], Els Wauters[82], Arthur A.M. Wilde[83,84], Ian Ford[85], David J. Stott[86], Ale Algra[87], Maria G. Andreassi[88], Diego Ardissino[89], Benoit J. Arsenault[90,91], Christie M. Ballantyne[13], Thomas O. Bergmeijer[92], Connie R. Bezzina[83], Simon C. Body[17,93], Peter Bogaty[94,95,96], Hermann Brenner[28], Ralph Burkhardt[79,97], Clara Carpeggiani[88], Gianluigi

Condorelli[62,98], Rhonda M. Cooper-DeHoff[36], Sharon Cresci[44,99], Ulf de Faire[11], Robert N. Doughty[100], Heinz Drexel[41,42,101], James C. Engert[33,102,103], Keith A.A. Fox[104], Domenico Girelli[48], Emil Hagström[9,10], Stanley L. Hazen[56,105], Claes Held[9,10], Harry Hemingway[72], Imo E. Hoefer[106], G. Kees Hovingh[107], Julie A. Johnson[36,108], J. Wouter Jukema[59,109,110], Marcin P. Kaczor[111], Mika Kähönen[112,113], Jiri Kettner[114], Marek Kiliszek[115], Olaf H. Klungel[22], Bo Lagerqvist[9,73], Diether Lambrechts[24,25], Jari O. Laurikka[116,117], Terho Lehtimäki[46,47], Daniel Lindholm[9,10], B. K. Mahmoodi[92], Anke H. Maitland-van der Zee[22,118], Ruth McPherson[60,119], Olle Melander[19,120], Andres Metspalu[20,21], Anna Niemcunowicz-Janica[121], Oliviero Olivieri[48], Grzegorz Opolski[122], Colin N. Palmer[123], Gerard Pasterkamp[124], Carl J. Pepine[108], Alexandre C. Pereira[30], Louise Pilote[23,125], Arshed A. Quyyumi[77], A. Mark Richards[51,126], Marek Sanak[111], Markus Scholz[79,127], Agneta Siegbahn[9,128], Juha Sinisalo[129], J.Gustav Smith[130,131], John A. Spertus[132,133], Alexandre F. R. Stewart[60,61], Wojciech Szczeklik[111], Anna Szpakowicz[15], Jurriën M. ten Berg[92], George Thanassoulis[33,23,103], Joachim Thiery[79,134], Yolanda van der Graaf[135], Frank L.J. Visseren[136], Johannes Waltenberger[137], CARDIoGRAMPlusC4D, Pim Van der Harst[138], Jean-Claude Tardif[31,32], Naveed Sattar[86], Chim C. Lang[45], Guillaume Pare[139,140], James M. Brophy[23,125], Jeffrey L. Anderson[5,66], Winfried März[29,142,143], Lars Wallentin[9,73], Vicky A. Cameron[51],* Benjamin D. Horne[5,141],* Nilesh J. Samani[26,27],* Aroon Hingorani[1],* Folkert W. Asselbergs[1,3,144]*

The GENIUS-CHD Consortium Affiliations

[1]Institute of Cardiovascular Science, Faculty of Population Health Science, University College London, London, UK

[2]Bart's Heart Centre, St Bartholomew's Hospital, London, EC1A2DA

[3]Department of Cardiology, Division Heart and Lungs, UMC Utrecht, Utrecht, Netherlands

[4]Groningen Research Institute of Pharmacy, University of Groningen, Groningen, the Netherlands

[5]Intermountain Heart Institute, Intermountain Medical Center, Salt Lake City, UT

[6]Clinical Trial Service Unit and Epidemiological Studies Unit, Nuffield Department of Population Health, University of Oxford, Oxford, UK.

[7]Medical Research Council Population Health Research Unit at the University of Oxford, Oxford, UK

[8]National Institute for Health Research Oxford Biomedical Research Centre, Oxford University Hospital, Oxford, UK

[9]Uppsala Clinical Research Center, Uppsala, Sweden

[10]Department of Medical Sciences, Cardiology, Uppsala University, Uppsala, Sweden.

[11]Institute of Environmental Medicine, Box 210, Karolinska Institutet, 171 77 Stockholm, Sweden

[12]Section of Cardiology, Michael E. DeBakey Veterans Affairs Medical Center

[13]Section of Cardiovascular Research, Department of Medicine, Baylor College of Medicine, Houston, TX, USA

[14]Department of Population Medicine and Civilization Disease Prevention; Medical University of Bialystok

[15]Department of Cardiology; Medical University of Bialystok

[16]Department of Anesthesiology, Perioperative and Pain Medicine, Brigham & Women's Hospital, Boston, MA 02115, USA

[17]Harvard Medical School

[18]Departments of Preventive Medicine and Biochemistry and Molecular Medicine, Keck School of Medicine of USC, Los Angeles, CA 90033

[19]Department of Clinical Sciences, Lund University, Malmö, Sweden

[20]Estonian Genome Center, Institute of Genomics, University of Tartu

[21]Department of Biotechnology, Institute of Molecular and Cell Biology, University of Tartu, Tartu, Estonia

[22]Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht University

[23]Centre for Outcomes Research & Evaluation, Research Institute of the McGill University Health Centre, Montreal, 5252 De Maisonneuve Boulevard, Quebec, Canada, H4A 3S5

[24]Laboratory for Translational Genetics, Department of Human Genetics, KU Leuven, Belgium

[25]Laboratory for Translational Genetics, VIB Center for Cancer Biology, VIB, Belgium

[26]Department of Cardiovascular Sciences, University of Leicester, BHF Cardiovascular Research Centre, Glenfield Hospital, Leicester, UK

[27]NIHR Leicester Biomedical Research Centre, Glenfield Hospital, Groby Road, Leicester, LE3 9QP

[28]Division of Clinical Epidemiology and Aging Research, German Cancer Research Center (DKFZ), Im Neuenheimer Feld 581, 69120 Heidelberg, Germany

[29]Vth Department of Medicine, Medical Faculty Mannheim, Heidelberg University, Theodor-Kutzer-Ufer 1-3, 68167 Mannheim, Germany

[30]Heart Institute, University of Sao Paulo

[31]Montreal Heart Institute, 5000 Belanger St., Montreal QC, H1T1C8, Canada

[32]Université de Montréal, Faculty of Medicine, 29000 blvd Edouard-Montpetit, Montreal QC, H3T1J4, Canada

[33]Preventive and Genomic Cardiology, McGill University Health Center, Montreal, Quebec, Canada

[34]Institute for Biomedicine, Eurac Research, Affiliated Institute of the University of Lübeck, Bolzano, Italy

[35]Laboratory of Experimental Cardiology, UMC Utrecht, the Netherlands

[36]University of Florida, Department of Pharmacotherapy and Translational Research and Center for Pharmacogenomics, 1333 Center Drive, Gainesville FL, USA 32608-0486

[37]Institute for Genetic Medicine, Keck School of Medicine of USC, Los Angeles, CA 90033

[38]Centre for Experimental Medicine, Institut for Clinical and Experimental Medicine, Prague, Czech Republic

[39]Department of Cardio-Thoracic Surgery, Finnish Cardiovascular Research Center - Tampere, Faculty of Medicine and Life Sciences, University of Tampere, Arvo Ylpön katu 34, Tampere 33014, Finland

[40]Department of Biostatistics &Epidemiology, Texas Heart Institute, Houston, TX, USA

[41]Vorarlberg Institute for Vascular Investigation and Treatment (VIVIT), Carinagasse 47, 6800 Feldkirch, Austria

[42]Private University of the Principality of Liechtenstein, Dorfstrasse 24, 9495 Triesen, Liechtenstein

[43]Medical Central Laboratories, Carinagasse 47, 6800 Feldkirch, Austria

[44]Washington University School of Medicine, Department of Genetics, Statistical Genomics Division, Saint Louis, Missouri

[45]Division of Molecular & Clinical Medicine, School of Medicine, University of Dundee, Dundee DD1 9SY, Scotland, U.K.

[46]Department of Clinical Chemistry, Fimlab Laboratories, Arvo Ylpön katu 34, Tampere 33014, Finland

[47]Department of Clinical Chemistry, Finnish Cardiovascular Research Center - Tampere, Faculty of Medicine and Life Sciences, University of Tampere, Tampere 33014, Finland

[48]Department of Medicine, University of Verona, Italy

[4]Department of Cardiology, Heart Center, Tampere University Hospital, Arvo Ylpön katu 6, Tampere 33521, Finland

[50]Department of Cardiology, Finnish Cardiovascular Research Center - Tampere, Faculty of Medicine and Life Sciences, University of Tampere, Tampere 33014, Finland

[51]The Christchurch Heart Institute, University of Otago Christchurch, PO Box 4345, Christchurch 8140, New Zealand

[52]Department of Medical Genetics, Medical University of Warsaw, Pawinskiego 3c, 02-106 Warsaw, Poland

[53]Department of Epidemiology, Emory University Rollins School of Public Health, 1518 Clifton Rd. NE, Atlanta, GA 30322, United States

[54]Department of Biomedical Informatics, Emory University School of Medicine, Atlanta, GA 30322, United States

[55]Amsterdam UMC, University of Amsterdam, Clinical Epidemiology and Biostatistics, The Netherlands

[56]Department of Cellular and Molecular Medicine, Lerner Research Institute, Cleveland Clinic, OH 44106

[57]Department of Cardiovascular Medicine, Heart and Vascular Institute, and Center for Clinical Genomics, Cleveland Clinic, OH 44106

[58]Section of gerontology and geriatrics, Department of internal medicine, Leiden University Medical Center, Leiden, The Netherlands

[59]Department of Cardiology, Leiden, University Medical Center, Leiden, the Netherlands

[60]Ruddy Canadian Cardiovascular Genetics Centre, University of Ottawa Heart Institute, Ottawa, Ontario, Canada

[61]Department of Biochemistry, Microbiology and Immunology, University of Ottawa, Ontario, Canada

[62]Department of Cardiovascular Medicine, Humanitas Clinical and Research Center, Via Manzoni 56, Rozzano, 20089 Milan, Italy.

[63]Transplantation Laboratory, Medicum, University of Helsinki, Helsinki, Finland.

[64] University of Texas School of Public Health, Houston, TX, USA

[65]Clinica Mediterranea, Naples, Italy.

[66]Cardiology Division, Department of Internal Medicine, University of Utah, Salt Lake City, UT

[67]Cardiovascular Sciences, University of Edinburgh, QMRI, 47 Little France Crescent, Edinburgh EH16 4TJ

[68]ATS Sardegna, ASL 3 Nuoro

[69]William Harvey Research Institute, Barts &the London Medical School, Queen Mary University of London, London, UK

[70]Centre for Genomic Health, Queen Mary University of London, London, UK.

[71]Department of Health Sciences, University of Leicester, UK.

[72]Institute of Health Informatics, Faculty of Population Health Science, University College London, London, UK

[73]Department of Medical Sciences, Cardiology, Uppsala University, Uppsala, Sweden

[74]Centro de Pesquisa Clinica, Hospital Universitario, Universidade de Sao Paulo

[75]Cardiovascular Research Center and Center for Human Genetic Research, Massachusetts General Hospital, Boston, Massachusetts; Program in Medical and Population Genetics, Broad Institute, Cambridge, Massachusetts.

[76]Department of Medicine and Cardiology, Academic Teaching Hospital Feldkirch, Carinagasse 47, 6800 Feldkirch, Austria

[77]Division of Cardiology, Department of Medicine, Emory Clinical Cardiovascular Research Institute, Emory University School of Medicine. 1462 Clifton Rd NE, Suite # 513, Atlanta, GA 30322 United States

[78]Heart Center Leipzig, Leipzig, Germany

[79]LIFE Research Center for Civilization Diseases, University of Leipzig, Leipzig, Germany

[80]Bart's Heart Centre, St Bartholomew's Hospital, London, EC1A7BE

[81]Departement of Cardiovascular Sciences , KU Leuven, Belgium

[82]Respiratory Oncology Unit, Department of Respiratory Medicine, University Hospitals KU Leuven, Leuven, Belgium.

[83]Amsterdam UMC, University of Amsterdam, Clinical and Experimental Cardiology, Amsterdam Cardiovascular Sciences, AMC Heart Center, the Netherlands.

[84]Princess Al-Jawhara Al-Brahim Centre of Excellence in Research of Hereditary Disorders, Jeddah, Saudi Arabia.

[85]Robertson Center for Biostatistics, University of Glasgow, United Kingdom

[86]Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK

[87]Department of Neurology&Neurosurgery, Brain Centre Rudolf Magnus and Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht and Utrecht University,

Utrecht, The Netherlands

[88]CNR Institute of Clinical Physiology, via Moruzzi, 1- 56124 Pisa Italy

[89] Cardiology Department, Parma University Hospital, Parma, Italy

[90]Centre de recherche de l'Institut Universitaire de cardiologie et de pneumologie de Québec

[91]Department of Medicine, Faculty of Medicine, Université Laval, Québec, Canada

[92]St. Antonius Hospital, dept. Cardiology, Koekoekslaan 1, 3435CM, Nieuwegein, The Netherlands

[93]Department of Anesthesia, Pain and Critical Care, Beth Israel Deaconess Medical Center, Boston, MA 02215, USA

[94]Service de cardiologie, Département multidisciplinaire de cardiologie, Institut universitaire de cardiologie et de pneumologie de Québec, 2725 Chemin Ste-Foy, Québec City, Québec G1V 4G5, Canada

[95]Unité d'évaluation cardiovasculaire, Institut national d'excellence en santé et en services sociaux (INESSS), Montreal, Québec, Canada

[96]Laval University, Institut universitaire de cardiologie et de pneumologie de Québec, Québec City, Québec, Canada

[97]Institute of Clinical Chemistry and Laboratory Medicine, University Hospital Regensburg, Germany

[98]Department of Biomedical Sciences, Humanitas University, Via Manzoni 113, Rozzano, 20089 Milan, Italy.

[99]Washington University School of Medicine, Department of Medicine, Cardiovascular Division, Saint Louis, Missouri

[100]Heart Health Research Group, University of Auckland, Private Bag 92019, Auckland 1142,

New Zealand

[101]Drexel University College of Medicine, 245 N. 15th Street, Philadelphia PA 19102, USA

[102]Research Institute of the McGill University Health Centre, Montreal, 1001 Decarie Boulevard, Office EM1-2218, Quebec, Canada, H4A 3J1

[103]Division of Cardiology, Department of Medicine, Royal Victoria Hospital, McGill University Health Centre, Montreal, Quebec, Canada

[104]Emeritus Professor of Cardiology, University of Edinburgh

[105]Department of Cardiovascular Medicine, Heart and Vascular Institute, and Center for Microbiome and Human Health, Cleveland Clinic, OH 44106

[106]Department of Clinical Chemistry and Hematology, UMC Utrecht, the Netherlands

[107]Department of Vascular Medicine, Academic Medical Center, Amsterdam, The Netherlands.

[108]University of Florida, College of Medicine, Division of Cardiovascular Medicine, 1600 SW Archer Road/Box 100277, Gainesville FL, USA 32610-0277

[109]Einthoven Laboratory for Experimental Vascular Medicine, LUMC, Leiden, the Netherlands

[110]Interuniversity Cardiology Institute of the Netherlands, Utrecht, The Netherlands

[111]Department of Internal Medicine, Jagiellonian University Medical College, 8 Skawinska Str, 31-066 Kraków, Poland

[112]Department of Clinical Physiology, Tampere University Hospital, FM1 3rd floor, Tampere 33521, Finland

[113]Department of Clinical Physiology, Finnish Cardiovascular Research Center - Tampere, Faculty of Medicine and Life Sciences, University of Tampere, Tampere 33014, Finland

[114]Cardiology Centre, Institute for Clinical and Experimental Medicine, Prague, Czech Republic

[115]Department of Cardiology and Internal Diseases, Military Institute of Medicine, ul. Szaserów

128, 04–141 Warsaw, Poland

[116]Department of Cardio-Thoracic Surgery, Heart Center, Tampere University Hospital, Arvo Ylpön katu 6, Tampere 33521, Finland

[117]Department of Cardio-Thoracic Surgery, Finnish Cardiovascular Research Center - Tampere, Faculty of Medicine and Life Sciences, University of Tampere, Tampere 33014, Finland

[118]Department of Respiratory Medicine, Academic Medical Center, University of Amsterdam

[119]Departments of Medicine and Biochemistry, Microbiology and Immunology, University of Ottawa, Ontario, Canada

[120]Department of Internal Medicine, Skåne University Hospital, Malmö, Sweden

[121]Department of Forensic Medicine; Medical University of Bialystok

[122]1st Chair and Department of Cardiology, Medical University of Warsaw, ul. Banacha 1a, 02-097 Warsaw, Poland

[123]Pat Macpherson Centre for Pharmacogenetics and Pharmacogenomics, Division of Molecular & Clinical Medicine, Level 5, Mailbox 12, Ninewells Hospital and Medical School, Dundee, DD1 9SY

[124]Department of Clinical Chemistry, UMC Utrecht, the Netherlands

[125]Department of Medicine, McGill University Health Centre, 1001 Decarie Boulevard, Montreal, Québec, Canada

[126]Cardiovascular Research Institute, National University of Singapore, 1 E Kent Ridge Road, Singapore 119228

[127]Institute for Medical Informatics, Statistics and Epidemiology, University of Leipzig, Leipzig, Germany

[128]Department of Medical Sciences, Clinical Chemistry, Uppsala University, Uppsala, Sweden.

[129]Heart and Lung Center Helsinki University Hospital and University of Helsinki, Haartmaninkatu 4, 00029 HUS, Helsinki, Finland

[130]Department of Cardiology, Clinical Sciences, Lund University and Skåne University Hospital, Lund, Sweden

[131]Program in Medical and Population Genetics, Broad Institute, Cambridge, Massachusetts, USA

[132]Saint Luke's Mid America Heart Institute and the University of Missouri-Kansas City, Kansas City, Missouri

[133]4401 Wornall Road, 9th Floor, Kansas City, MO 64111

[134]Institute of Laboratory Medicine, Clinical Chemistry and Molecular Diagnostics, University Hospital, Leipzig, Germany

[135]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht and Utrecht University, Utrecht, The Netherlands

[136]Department of Vascular Medicine, University Medical Center Utrecht and Utrecht University, Utrecht, The Netherlands

[137]Department of Cardiovascular Medicine, University of Münster, Germany

[138]University Medical Center, University of Groningen, Groningen, The Netherlands

[139]McMaster University, Department of Pathology and Molecular Medicine

[140]Population Health Research Institute, Hamilton, ON L8L 2X2 Canada

[141]Department of Biomedical Informatics, University of Utah, Salt Lake City, UT

[142]Synlab academy, Synlab Holding Deutschland GmbH, Mannheim, Germany

[143]Clinical Institute of Medical and Chemical Laboratory Diagnostics, Medical University of Graz, Graz, Austria

[144]Durrer Centre Cardiogenetic Research, ICIN-Netherlands Heart Institute, Utrecht, Netherlands

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