

CHARGE Working Groups: Directory and Updates

**CHARGE
CONSORTIUM**

COHORTS FOR HEART & AGING RESEARCH
IN GENOMIC EPIDEMIOLOGY



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Adiposity

- A. Phenotypes: Body Mass Index (BMI), Waist to Hip Ratio (WHR), Waist Circumference (WC), Height (HT); Abdominal Fat (Visceral Adiposity Tissue, Subcutaneous Adipose Tissue), % Body Fat, ectopic fat (liver, pericardial)
- B. Phenotypes actively being analyzed
- C. WG Leaders: Ingrid Borecki lborecki@wustl.edu, L Adrienne Cupples adrienne@bu.edu, K. North kari_north@unc.edu, T Baranski baranski@wustl.edu
- D. Publications:

Y Ma, KL Tucker, CE Smith, YC Lee, T Huang, K Richardson, LD Parnell, CQ Lai, KL Young, AE Justice, Y Shao, KE North, JM Ordovás. 2014. Lipoprotein lipase variants interact with polyunsaturated fatty acids for obesity traits in women: Replication in two populations. Nutrition, Metabolism, and Cardiovascular Diseases 24(12):1323-39. PMID: 25156894.

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E. Grants:

Genetic Architecture of Adiposity in Large Cohorts (CHAPs). I. Borecki, PI, A. Cupples, MPI, K. North, MPI, T. Baranski, MPI. 2 R01 DK089256-05, 2014-2017.

Atrial Fibrillation/PR-Interval

- A. Phenotypes: Atrial Fibrillation and PR interval
- B. Phenotypes actively being analyzed
- C. WG Leaders: Emelia J. Benjamin emelia@bu.edu, Susan R. Heckbert heckbert@u.washington.edu,
Patrick T. Ellinor pellinor@partners.org

D. Publications:

Published: Integrating Genetic, Transcriptional, and Functional Analyses to Identify Five Novel Genes for Atrial Fibrillation. Sinner MF, Tucker NR, Lunetta KL, Ozaki K, Smith JG, Trompet S, Bis JC, Lin H, Chung MK, Nielsen JB, Lubitz SA, Krijthe BP, Magnani JW, Ye J, Gollob MH, Tsunoda T, Müller-Nurasyid M, Lichtner P, Peters A, Dolmatova E, Kubo M, Smith JD, Psaty BM, Smith NL, Jukema JW, Chasman DI, Albert CM, Ebana Y, Furukawa T, MacFarlane P, Harris TB, Darbar D, Dörr M, Holst AG, Svendsen JH, Hofman A, Uitterlinden A, Gudnason V, Isobe M, Malik R, Dichgans M, Rosand J, Van Wagoner DR; METASTROKE Consortium; AFGen Consortium, Benjamin EJ, Milan DJ, Melander O, Heckbert S, Ford I, Liu Y, Barnard J, Olesen MS, Stricker BH, Tanaka T, Kääb S, Ellinor PT. Circulation. 2014 Aug 14. pii: CIRCULATIONAHA.114.009892. [Epub ahead of print]

Targeted sequencing in candidate genes for atrial fibrillation: The Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Targeted Sequencing Study. Lin H, Sinner MF, Brody JA, Arking DE, Lunetta KL, Rienstra M, Lubitz SA, Magnani JW, Sotoodehnia N, McKnight B, McManus DD, Boerwinkle E, Psaty BM, Rotter JI, Bis JC, Gibbs RA, Muzny D, Kovar CL, Morrison AC, Gupta M, Folsom AR, Kääb S, Heckbert SR, Alonso A, Ellinor PT, Benjamin EJ. Targeted sequencing in candidate genes for atrial fibrillation: the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Targeted Sequencing Study. Heart Rhythm; 11: 452–7 (2014).

B-type natriuretic peptide and C-reactive protein in the prediction of atrial fibrillation risk: the CHARGE-AF Consortium of community-based cohort studies. Sinner MF, Stepas KA, Moser CB, Krijthe BP, Aspelund T, Sotoodehnia N, Fontes JD, Janssens AC, Kronmal RA, Magnani JW, Witteman JC, Chamberlain AM, Lubitz SA, Schnabel RB, Vasan RS, Wang TJ, Agarwal SK, McManus DD, Franco OH, Yin X, Larson MG, Burke GL, Launer LJ, Hofman A, Levy D, Gottdiener JS, Kääb S, Couper D, Harris TB, Astor BC, Ballantyne CM, Hoogeveen RC, Arai AE, Soliman EZ, Ellinor PT, Stricker BH, Gudnason V, Heckbert SR, Pencina MJ, Benjamin EJ, Alonso A. Europace. 2014 Jul 18. pii: euu175. [Epub ahead of print]

Sequencing of SCN5A identifies rare and common variants associated with cardiac conduction: Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium. Magnani JW, Brody JA, Prins BP, Arking DE, Lin H, Yin X, Liu CT, Morrison AC, Zhang F, Spector TD, Alonso A, Bis JC,

Heckbert SR, Lumley T, Sitlani CM, Cupples LA, Lubitz SA, Soliman EZ, Pulit SL, Newton-Cheh C, O'Donnell CJ, Ellinor PT, Benjamin EJ, Muzny DM, Gibbs RA, Santibanez J, Taylor HA, Rotter JI, Lange LA, Psaty BM, Jackson R, Rich SS, Boerwinkle E, Jamshidi Y, Sotoodehnia N; CHARGE Consortium; NHLBI Exome Sequencing Project (ESP); UK10K. *Circ Cardiovasc Genet.* 2014 Jun;7(3):365-73. doi: 10.1161/CIRCGENETICS.113.000098.

Novel genetic markers associate with atrial fibrillation risk in Europeans and Japanese. Lubitz SA, Lunetta KL, Lin H, Arking DE, Trompet S, Li G, Krijthe BP, Chasman DI, Barnard J, Kleber ME, Dörr M, Ozaki K, Smith AV, Müller-Nurasyid M, Walter S, Agarwal SK, Bis JC, Brody JA, Chen LY, Everett BM, Ford I, Franco OH, Harris TB, Hofman A, Kääb S, Mahida S, Kathiresan S, Kubo M, Launer LJ, Macfarlane PW, Magnani JW, McKnight B, McManus DD, Peters A, Psaty BM, Rose LM, Rotter JI, Silbernagel G, Smith JD, Sotoodehnia N, Stott DJ, Taylor KD, Tomaschitz A, Tsunoda T, Uitterlinden AG, Van Wagoner DR, Völker U, Völzke H, Murabito JM, Sinner MF, Gudnason V, Felix SB, März W, Chung M, Albert CM, Stricker BH, Tanaka T, Heckbert SR, Jukema JW, Alonso A, Benjamin EJ, Ellinor PT. *J Am Coll Cardiol.* 2014 Apr 1;63(12):1200-10. doi: 10.1016/j.jacc.2013.12.015. Epub 2014 Jan 30.

E. Grants: None at present

Aging and Longevity

- A. Phenotypes: Survival to age 90 years and older; Morbidity-free survival; Hand grip strength; Lower extremity strength; Walking speed; Healthy Aging Index, Genome-wide heterozygosity, mitochondrial copy number
- B. Phenotypes actively being analyzed
- C. WG Leaders: Joanne Murabito murabito@bu.edu
- D. Publications:

Newman AB, Walter S, Lunetta KL, Garcia ME, Slagboom PE, Christensen K et al. A meta-analysis of four genome-wide association studies of survival to age 90 years or older: the Cohorts for Heart and Aging Research in Genomic Epidemiology Consortium. *J Gerontol A Biol Sci Med Sci* 2010; 65(5):478-487.

Walter S, Atzmon G, Demerath EW, Garcia ME, Kaplan RC, Kumari M et al. A genome-wide association study of aging. *Neurobiology Aging* 2011; 32(11):2109-2128.

Kuningas M, Estrada K, Hsu YH, Nandakumar K, Uitterlinden AG, Lunetta KL et al. Large common deletions associate with mortality at old age. *Hum Mol Genet* 2011.

Walter S, Mackenbach J, Voko Z, Lhachimi S, Ikram MA, Uitterlinden AG et al. Genetic, Physiological, and Lifestyle Predictors of Mortality in the General Population. *Am J Public Health* 2012; 102(4):e3-e10.

Broer L, Demerath EW, Garcia ME, Homuth G, Kaplan RC, Lunetta KL, Tanaka T, Tranah GJ, Walter S, Arnold AM, Atzmon G, Harris TB, Hoffmann W, Karasik D, Kiel DP, Kocher T, Launer LJ, Lohman KK, Rotter JI, Tiemeier H, Uitterlinden AG, Wallaschofski H, Bandinelli S, Dorr M, Ferrucci L, Franceschini N, Gudnason V, Hofman A, Liu Y, Murabito JM, Newman AB, Oostra BA, Psaty BM, Smith AV, van Duijn CM. Association of heat shock proteins with all-cause mortality. *Age (Dordr)* 2012. PMID 22555621.

NIHMSID:436194.

Broer L, Buchman AS, Deelen J, Evans DS, Faul JD, Lunetta KL, Sebastiani P, Smith JA, Smith AV, Tanaka T, Yu L, Arnold AM, Aspelund T, Benjamin EJ, DeJager PL, Eirkisdottir G, Evans DA, Garcia ME, Hofman A, Kaplan RC, Kardia SLR, Kiel DP, Oostra BA, Orwoll ES, Parimi N, Psaty BM, Rivadeneira F, Rotter JI, Seshadri S, Singleton A, Tiemeier H, Uitterlinden AG, Zhao W, Bandinelli S, Bennett DA, Ferrucci L, Gudnason V, Harris TB, Karasik D, Launer, LJ, Perls TT, Slagboom PE, Tranah GJ, Weir DR, Newman AB, van Duijn CM, Murabito JM. GWAS of Longevity in CHARGE Consortium Confirms APOE and FOXO3 Candidacy. *J Gerontol A Biol Sci Med Sci* 2014

Bihlmeyer NA, Brody JA, Smith AV, et al. Genetic diversity is a predictor of mortality in humans. *BMC Genet.* 2014;15(1):159.

Minster RL, Sanders JL, Singh J, et al. Genome-Wide Association Study and Linkage Analysis of the Healthy Aging Index. *J Gerontol A Biol Sci Med Sci.* Mar 10 2015.

E. Grants: None at present

Blood Pressure

A. Phenotypes: systolic blood pressure, diastolic blood pressure, hypertension, mean arterial pressure, pulse pressure (actively analyzing all of the above phenotypes actively)

B. Phenotypes actively being analyzed

C. WG Leaders: Dan Levy levy@nhlbi.nih.gov, Georg Ehret georg@rhone.ch

D. Publications:

Levy D, Ehret GB, Rice K, Verwoert GC, Launer LJ et al. Genome-wide association study of blood pressure and hypertension. *Nat Genet.* 2009 Jun;41(6):677-87.

Johnson AD, Newton-Cheh C, Chasman DI et al. Association of hypertension drug target genes with blood pressure and hypertension in 86,588 individuals. *Hypertension.* 2011 May;57(5):903-10.

Ehret GB, Munroe PB, Rice KM, Bochud M, Johnson AD, et al. Genetic variants in novel pathways influence blood pressure and cardiovascular disease risk. *Nature.* 2011 Sep 11;478(7367):103-9.

Wain LV, Verwoert GC, O'Reilly PF, Shi G, et al. Genome-wide association study identifies six new loci influencing pulse pressure and mean arterial pressure. *Nat Genet.* 2011 Sep 11;43(10):1005-11.

Morrison AC, Bis JC, Hwang SJ, Ehret GB, Lumley T, Rice K, Muzny D, Gibbs RA, Boerwinkle E, Psaty BM, Chakravarti A, Levy D. Sequence Analysis of Six Blood Pressure Candidate Regions in 4,178 Individuals: The Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Targeted Sequencing Study. *PLoS One.* 2014 Oct 2;9(10):e10915

Ganesh SK, Chasman DI, Larson MG et al. Effects of long-term averaging of quantitative blood pressure traits on the detection of genetic associations. *Am J Hum Genet.* 2014 Jul 3;95(1):49-65

Simino J, Shi G, Bis JC, Chasman DI, Ehret GB, Gu X. et al. Gene-age interactions in blood pressure regulation: a large-scale investigation with the CHARGE, Global BPgen, and ICBP Consortia. *Am J Hum Genet.* 2014 Jul 3;95(1):24-38.

E. Grants:

NIH / NHLBI and many other funding organisms (for a complete listing see *Nature.* 2011 Sep 11;478(7367):103-9.).

CHARGE-S Analysis & Bioinformatics

- A. Phenotypes: No specific phenotypes. This WG discusses methods for analyzing sequence data.
- B. Phenotypes actively being analyzed
- C. WG Leaders: L. Adrienne Cupples adrienne@bu.edu, Thomas Lumley tlumley@u.washington.edu
- D. Publications:

Design of CHARGE Sequencing Study –

<http://stattech.wordpress.fos.auckland.ac.nz/files/2012/05/design-paper.pdf>

Lin H, Wang M, Brody JA, Bis JC, Dupuis J, Lumley T, McKnight B, Rice KM, Sitlani CM, Reid JG, Bressler J, Liu X, Davis BC, Johnson AD, O'Donnell CJ, Kovar CL, Dinh H, Wu Y, Newsham I, Chen H, Broka A, DeStefano AL, Gupta M, Lunetta KL, Liu CT, White CC, Xing C, Zhou Y, Benjamin EJ, Schnabel RB, Heckbert SR, Psaty BM, Muzny DM, Cupples LA, Morrison AC, Boerwinkle E. Strategies to design and analyze targeted sequencing data: cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium Targeted Sequencing Study. Circ Cardiovasc Genet. 2014 Jun;7(3):335-43. doi: 10.1161/CIRCGENETICS.113.000350. PMID: 24951659 PMCID: PMC4176824

Li AH, Morrison AC, Kovar C, Cupples LA, Brody JA, Polfus LM, Yu B, Metcalf G, Muzny D, Veeraraghavan N, Liu X, Lumley T, Mosley TH, Gibbs RA, Boerwinkle E. Analysis of loss-of-function variants and 20 risk factor phenotypes in 8,554 individuals identifies loci influencing chronic disease. Nat Genet. 2015 Jun;47(6):640-2. doi: 10.1038/ng.3270. Epub 2015 Apr 27. PMID: 25915599

- E. Grants: None at present

CHARGE mtDNA+

- A. Phenotypes: BMI, WHRadjBMI, GLUC, INS, HOMAB, HOMAIR and HbA1c
- B. Phenotypes actively being analyzed
- C. WG Leaders: Aldi Kraja aldi@dsgmail.wustl.edu, Chunyu Liu chunyu.liu@nih.gov, Symen Ligthart s.lighthart@erasmusmc.nl, Gavin Hudson gavin.hudson@newcastle.ac.uk, Kent Taylor ktaylor@labiomed.org, Ingrid Borecki lborecki@wustl.edu, James Meigs jmeigs@partners.org, and Jerome Rotter jrotter@labiomed.org
- D. Publications: none
- E. Grants: no information available at this time

Depression

- A. Phenotypes: Depressive symptoms
- B. Phenotypes actively being analyzed
- C. WG Leader: Henning Tiemeier h.tiemeier@erasmusmc.nl, Joanne Murabito murabito@bu.edu
- D. Publications:
Hek K, Demirkiran A, Lahti J, Terracciano A, Teumer A, Cornelis MC, Amin N, Bakshis E, Baumert J, Ding J, Liu Y, Marciante K, Meirelles O, Nalls MA, Sun YV, Vogelzangs N, Yu L, Bandinelli S, Benjamin EJ, Bennett DA, Boomsma D, Cannas A, Coker LH, de Geus E, De Jager PL, Diez-Roux AV, Purcell S, Hu FB, Rimm EB, Hunter DJ, Jensen MK, Curhan G, Rice K, Penman AD, Rotter JI, Sotoodehnia N, Emeny R, Eriksson JG, Evans DA, Ferrucci L, Fornage M, Gudnason V, Hofman A, Illig T, Kardia S, Kelly-Hayes M, Koenen K, Kraft P, Kuningas M, Massaro JM, Melzer D, Mulas A, Mulder CL, Murray A, Oostra BA, Palotie A, Penninx B, Petersmann A, Pilling LC, Psaty B, Rawal R, Reiman EM, Schulz A, Shulman JM, Singleton AB, Smith AV, Sutin AR, Uitterlinden AG, Volzke H, Widen E, Yaffe K, Zonderman AB, Cucca F, Harris T, Ladwig KH, Llewellyn DJ, Raikkonen K, Tanaka T, van Duijn CM, Grabe HJ, Launer LJ, Lunetta KL, Mosley TH, Jr., Newman AB, Tiemeier H, Murabito J. A genome-wide association study of depressive symptoms. *Biological psychiatry*. 2013;73:667-678
- E. Grants: None at present

Echocardiography: EchoGen

- A. Phenotypes: Echocardiography measures, including LV mass, internal dimensions, wall thickness, LA size, aortic root size, fractional shortening and qualitative LV systolic function; doppler measures of mitral E-wave velocity, A-wave velocity, E/A ratio, deceleration time and isovolumetric relaxation time; tissue Doppler and pulmonary venous flow phenotype data available in limited cohorts
- B. Phenotypes actively being analyzed: “Iterative MA project”: LV mass, internal dimensions, wall thickness, LA diameter, aortic root diameter, fractional shortening, LV systolic function; “Diastolic function project”: Mitral E-wave velocity, A-wave velocity, E/A ratio, deceleration time, isovolumetric relaxation time, diastolic dysfunction defined in multiple ways; Iterative MA project phenotypes analyzes stratified on hypertension-status
- C. WG Leaders: Vasan Ramachandran vasan@bu.edu, Janine Felix j.felix@erasmusmc.nl
- D. Publications:

Vasan RS, et al. Genetic variants associated with cardiac structure and function: a meta-analysis and replication of genome-wide association data. JAMA. 2009 Jul 8;302(2):168-78.

- E. Grants:

Collaboration with Drs. Capolla and Margulies on their recently funded R01, “Integrative Genomics of Human Heart Failure”. The goals of this proposal are to use integrative genomics to test whether transcriptional regulatory programs identified in animal models are relevant in human HF and to perform unbiased screens to identify previously unknown regulators of myocardial gene expression in humans. EchoGen will provide access to meta-analysis data and we will test the top 100 most consistently associated eSNPs that emerge from Aims 1 and Aim2 of the grant with echocardiographic phenotypes in EchoGen.

Educational Attainment

- A. Phenotypes: educational attainment
- B. Phenotypes actively being analyzed: years of education, college degree
- C. WG Leaders: Philipp Koellinger koellinger@ese.eur.nl, David Cesaroni dac12@nyu.edu, Daniel Benjamin daniel.benjamin@gmail.com

D. Publications:

Rietveld, C.A., Medland, S.E., Derringer, J., Yang, J., Esko, T., ... Koellinger, P.D. (2013). GWAS of 126,559 individuals identifies genetic variants associated with educational attainment. *Science*, 240(6139), 1467-1471.

Rietveld, C.A., Esko, T., Davies, G., Pers, T.H., Turley, P.A., Benyamin, B., ..., Koellinger, P.D. (2014). Common genetic variants associated with cognitive performance identified using proxy-phenotype method. *Proceedings of the National Academy of Sciences of the United States of America*, 111(38), 13790-13794.

Ward, M., McMahon, G., St Pourcain, B., Evans, D.M., Rietveld, C.A., Benjamin, D.J., Koellinger, P.D., Cesaroni, D., The Social Science Genetic Association Consortium, Davey Smith, G., Timpson, N.J. (2014). "Genetic variation associated with differential educational attainment in adults has anticipated associations with school performance in children", *PLoS ONE* 9(7): e100248.

Rietveld, C. A., Conley, D., Eriksson, N., Esko, T., Medland, S. E., Vinkhuyzen, A. A. E., ... Social Science Genetic Association Consortium. (2014). Replicability and robustness of GWAS for behavioral traits. *Psychological Science*, 25(11), 1975-1986.

de Zeeuw, E.L., et al., (2014), "Polygenic Scores Associated With Educational Attainment in Adults Predict Educational Achievement and Attention Problems in Children", *Am J Med Genet Part B*, 9999, 1–11.

E. Grants:

This work is supported by funding from the Söderbergh Foundation (E9/11), the Swedish Research Council (421-2013-1061), The Jan Wallander and Tom Hedelius Foundation, an ERC Consolidator Grant (647648 EdGe – Philipp Koellinger), the Pershing Square Fund of the Foundations of Human Behavior, and the NIA/NIH through grants P01-AG005842, P01-AG005842-20S2, P30-AG012810, and T32-AG000186-23 to NBER.CHARGE meeting in Los Angeles, the 2012 Iceland CHARGE meeting in Reykjavik and the 2013 CHARGE meeting in Rotterdam.

EKG

- A. Phenotypes: EKG related phenotypes, including QT, QRS, RR
- B. Phenotypes actively being analyzed:
- C. WG Leaders: Christopher Newton-Cheh CNEWTONCHEH@mgh.harvard.edu, Mark Eijgelsheim m.eijgelsheim@erasmusmc.nl, Nona Sotoodehnia nsotoo@u.washington.edu
- D. Publications:

Sequencing of SCN5A identified rare and common variants associated with cardiac conduction: Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium. Circ Cardiovascular Genetics. 2014 Jun;7(3):365-73.

Genetic association study of QT interval highlights calcium signaling pathways in myocardial repolarization. Nat Genet. 2014 Aug;46(8):826-36. doi: 10.1038/ng.3014. Epub 2014 Jun 22. Identification of heart rate-associated loci and their effects on cardiac conduction and rhythm disorders. Nat Genet. 2013 Apr 14. doi: 10.1038/ng.2610. [Epub ahead of print]

Common variants in 22 loci are associated with QRS duration and cardiac ventricular conduction. Nature Genetics Volume:42,Pages:1068–1076 .2010)

Genome-wide association analysis identifies multiple loci related to resting heart rate. Hum Mol Genet. 2010 Oct 1;19(19):3885-94. Epub 2010 Jul 16.

Common variants at ten loci influence QT interval duration in the QTGEN Study. Nature Genetics 41, 399 - 406 (2009)

- E. Grants:

Genomics of Cardiac Electrical Activity and Arrhythmias. NHLBI R01 2013-2017. Multiple PIs from CHARGE EKG working group.

Endothelial Function

- A. Phenotypes: brachial artery flow-mediated dilation
- B. Phenotypes actively being analyzed: Brachial artery diameter, flow-mediated dilation (maximum, 60 sec), volume plethysmographic peripheral arterial tonometry (pulse wave amplitude)
- C. WG Leaders: Renate B. Schnabel schnabel@bu.edu, Naomi Hamburg Naomi.hamburg@bmc.org, Nicholas Smith nlsmith@u.washington.edu,
- D. Publications: none
- E. Grants:

Deutsche Forschungsgemeinschaft (German Research Foundation) Emmy Noether Program SGN
1149/3-1

Entrepreneurship

A. Phenotypes: Self-employment (at least once self-employment; serial self-employment) At least once self-employment; serial self-employment

B. Phenotypes actively being analyzed:

C. WG Leaders: Roy Thurik thurik@few.eur.nl, Albert Hofman a.hofman@erasmusmc.nl

D. Publications:

Genome-wide association for loci influencing entrepreneurial behavior: The Rotterdam Study, *Behavior Genetics*, 2008, 38, 628–629.

Genome-wide association studies and the genetics of entrepreneurship, *European Journal of Epidemiology*, 2010, 25, 1–3.

Genome-wide association studies in economics and entrepreneurship research: Promises and limitations, *Small Business Economics*, 2010, 35, 1–18.

Candidate gene studies and the quest for the entrepreneurial gene. *Small Business Economics*, 2011, 37, 269–275.

The molecular genetic architecture of self-employment. *PLOS ONE*, 2013, 8(4), e60542.

E. Grants:

Two grants from EIM/Panteia of €4000 each for short contracts of Matthijs van der Loos and Niels Rietveld prior to their PhD student appointments.

Epigenetics

- A. Phenotypes: DNA methylation and their relationship to cardiovascular risk factors and aging
- B. Phenotypes actively being analyzed:
- C. WG Leaders: Myriam Fornage Myriam.Fornage@uth.tmc.edu, Lisette Stolk L.stolk@erasmusmc.nl
- D. Publications: none
- E. Grants: none

Exome Chip

- A. Phenotypes: This subcommittee's primary focus is practical issues related to coordination of efforts in widespread genotyping, calling, and quality control of variants using Illumina's ExomeChip. It is also working on "incidental"/actionable findings.
- B. Phenotypes actively being analyzed:
- C. WG Leaders: Jerome Rotter Jrotter@labiomed.org, Chris O'Donnell odonnellc@nhlbi.nih.gov, Bruce Psaty psaty@u.washington.edu, and Steve Rich ssr4n@eservices.virginia.edu

D. Publications:

Grove ML, Yu B, Cochran BJ, Haritunians T, Bis JC, Taylor KD, Hansen M, Borecki IB, Cupples LA, Fornage M, Gudnason V, Harris TB, Kathiresan S, Kraaij R, Launer LJ, Levy D, Liu Y, Mosley T, Peloso GM, Psaty BM, Rich SS, Rivadeneira F, Siscovick DS, Smith AV, Uitterlinden A, van Duijn CM, Wilson JG, O'Donnell CJ, Rotter JI, Boerwinkle E. Best practices and joint calling of the HumanExome BeadChip: the CHARGE Consortium. PLoS One. 2013 Jul 12;8(7):e68095.

Peloso GM, Auer PL, Bis JC, Voorman A, Morrison AC, Stitzel NO, Brody JA, Khetarpal SA, Crosby JR, Fornage M, Isaacs A, Jakobsdottir J, Feitosa MF, Davies G, Huffman JE, Manichaikul A, Davis B, Lohman K, Joon AY, Smith AV, Grove ML, Zanoni P, Redon V, Demissie S, Lawson K, Peters U, Carlson C, Jackson RD, Ryckman KK, Mackey RH, Robinson JG, Siscovick DS, Schreiner PJ, Mychaleckyj JC, Pankow JS, Hofman A, Uitterlinden AG, Harris TB, Taylor KD, Stafford JM, Reynolds LM, Marioni RE, Dehghan A, Franco OH, Patel AP, Lu Y, Hindy G, Gottesman O, Bottinger EP, Melander O, Orho-Melander M, Loos RJ, Duga S, Merlini PA, Farrall M, Goel A, Asselta R, Girelli D, Martinelli N, Shah SH, Kraus WE, Li M, Rader DJ, Reilly MP, McPherson R, Watkins H, Ardissono D; NHLBI GO Exome Sequencing Project, Zhang Q, Wang J, Tsai MY, Taylor HA, Correa A, Griswold ME, Lange LA, Starr JM, Rudan I, Eiriksdottir G, Launer LJ, Ordovas JM, Levy D, Chen YD, Reiner AP, Hayward C, Polasek O, Deary IJ, Borecki IB, Liu Y, Gudnason V, Wilson JG, van Duijn CM, Kooperberg C, Rich SS, Psaty BM, Rotter JI, O'Donnell CJ, Rice K, Boerwinkle E, Kathiresan S, Cupples LA. Association of low-frequency and rare coding-sequence variants with blood lipids and coronary heart disease in 56,000 whites and blacks. Am J Hum Genet 2014 Feb 6;94(2):223-32.

Lange LA, Hu Y, Zhang H, Xue C, Schmidt EM, Tang ZZ, Bizon C, Lange EM, Smith JD, Turner EH, Jun G, Kang HM, Peloso G, Auer P, Li KP, Flannick J, Zhang J, Fuchsberger C, Gaulton K, Lindgren C, Locke A, Manning A, Sim X, Rivas MA, Holmen OL, Gottesman O, Lu Y, Ruderfer D, Stahl EA, Duan Q, Li Y, Durda P, Jiao S, Isaacs A, Hofman A, Bis JC, Correa A, Griswold ME, Jakobsdottir J, Smith AV, Schreiner PJ, Feitosa MF, Zhang Q, Huffman JE, Crosby J, Wassel CL, Do R, Franceschini N, Martin LW, Robinson JG, Assimes TL, Crosslin DR, Rosenthal EA, Tsai M, Rieder MJ, Farlow DN, Folsom AR, Lumley T, Fox ER, Carlson CS, Peters U, Jackson RD, van Duijn CM, Uitterlinden AG, Levy D, Rotter JI, Taylor HA, Gudnason V Jr, Siscovick DS, Fornage M, Borecki IB, Hayward C, Rudan I, Chen YE,

Bottiger EP, Loos RJ, Sætrom P, Hveem K, Boehnke M, Groop L, McCarthy M, Meitinger T, Ballantyne CM, Gabriel SB, O'Donnell CJ, Post WS, North KE, Reiner AP, Boerwinkle E, Psaty BM, Altshuler D, Kathiresan S, Lin DY, Jarvik GP, Cupples LA, Kooperberg C, Wilson JG, Nickerson DA, Abecasis GR, Rich SS, Tracy RP, Willer CJ; NHLBI Grand Opportunity Exome Sequencing Project. Whole-exome sequencing identifies rare and low-frequency coding variants associated with LDL cholesterol. *Am J Hum Genet* 2014 Feb 6:94(2):233-45.

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E. Grants:

Exome Chip CHARGE wiki page: <http://depts.washington.edu/chargeco/wiki/ExomeChip>

Eye Retina

A. Phenotypes: Retinal vessel diameter, retinopathy, early macular degeneration

B. Phenotypes actively being analyzed:

C. WG Leaders: Tien Y Wong tien_yin_wong@nuhs.edu.sg

D. Publications:

Ikram MK, Sim X, Jensen RA, Cutch MF, Hewitt AW, Ikram MA, Wang JJ, Klein R, Klein BE, Breteler MM, Cheung N, Liew G, Mitchell P, Uitterlinden AG, Rivadeneira F, Hofman A, de Jong PT, van Duijn CM, Kao L, Cheng CY, Smith AV, Glazer NL, Lumley T, McKnight B, Psaty BM, Jonasson F, Eiriksdottir G, Aspelund T; Global BPgen Consortium, Harris TB, Launer LJ, Taylor KD, Li X, Iyengar SK, Xi Q, Sivakumaran TA, Mackey DA, Macgregor S, Martin NG, Young TL, Bis JC, Wiggins KL, Heckbert SR, Hammond CJ, Andrew T, Fahy S, Attia J, Holliday EG, Scott RJ, Islam FM, Rotter JI, McAuley AK, Boerwinkle E, Tai ES, Gudnason V, Siscovick DS, Vingerling JR, Wong TY. Four novel Loci (19q13, 6q24, 12q24, and 5q14) influence the microcirculation in vivo. *PLoS Genet.* 2010 Oct 28;6(10):e1001184.

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Scott RJ, Viswanathan A; Global BPGen Consortium, Li G, Smith NL, Wiggins KL, Kuo JZ, Taylor KD, Hewitt AW, Martin NG, Montgomery GW, Sun C, Young TL, Mackey DA, van Zuydam NR, Doney AS, Palmer CN, Morris AD, Rotter JI, Tai ES, Gudnason V, Vingerling JR, Siscovick DS, Wang JJ, Wong TY. Genetic loci for retinal arteriolar microcirculation. *PLoS One.* 2013;8(6):e65804.

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E. Grants: none

Family Studies

- A. Phenotypes:
- B. Phenotypes actively being analyzed:
- C. WG Leaders: David Siscovick dsiscovick@nyam.org, Chris O'Donnell odonnellc@nhlbi.nih.gov,
Cashell Jaquish cashell.jaquish@nih.gov
- D. Publications: none
- E. Grants: none

Fatty Acid

- A. Phenotypes: Biomarker measures of different fatty acids, such as in plasma phospholipids or erythrocyte membranes
- B. Phenotypes actively being analyzed: Fatty Acids, HDL, Triglycerides
- C. WG Leaders: Rozenn Lemaitre rozenl@uw.edu, Dariush Mozaffarian dmozaffa@hsph.harvard.edu, Aaron Isaacs a.isaacs@erasmusmc.nl
- D. Publications

Smith CE, Follis JL, Nettleton JA, Foy M, Wu JH, Ma Y, Tanaka T, Manichakul AW, Wu H, Chu AY, Steffen LM, Fornage M, Mozaffarian D, Kabagambe EK, Ferruci L, Chen YI, Rich SS, Djoussé L, Ridker PM, Tang W, McKnight B, Tsai MY, Bandinelli S, Rotter JI, Hu FB, Chasman DI, Psaty BM, Arnett DK, King IB, Sun Q, Wang L, Lumley T, Chiuve SE, Siscovick DS, Ordovás JM, Lemaitre RN. Dietary fatty acids modulate associations between genetic variants and circulating fatty acids in plasma and erythrocyte membranes: Meta-analysis of nine studies in the CHARGE consortium. Mol Nutr Food Res. 2015 Jan 27. doi: 10.1002/mnfr.201400734.

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Guan W, Steffen BT, Lemaitre RN, Wu JH, Tanaka T, Manichaikul A, Foy M, Rich SS, Wang L, Nettleton JA, Tang W, Gu X, Bandinelli S, King IB, McKnight B, Psaty BM, Siscovick D, Djousse L, Chen YD, Ferrucci L, Fornage M, Mozaffarian D, Tsai MY, Steffen LM. Genome-wide association study of plasma N6 polyunsaturated fatty acids within the cohorts for heart and aging research in genomic epidemiology consortium. Circ Cardiovasc Genet. 2014 Jun;7(3):321-31.

Wu JH, Lemaitre RN, Manichaikul A, Guan W, Tanaka T, Foy M, Kabagambe EK, Djousse L, Siscovick D, Fretts AM, Johnson C, King IB, Psaty BM, McKnight B, Rich SS, Chen YD, Nettleton JA, Tang W,

Bandinelli S, Jacobs DR Jr, Browning BL, Laurie CC, Gu X, Tsai MY, Steffen LM, Ferrucci L, Fornage M, Mozaffarian D. Genome-wide association study identifies novel loci associated with concentrations of four plasma phospholipid fatty acids in the de novo lipogenesis pathway: results from the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium. *Circ Cardiovasc Genet.* 2013;6:171-83

Lemaitre RN, Tanaka T, Tang W, Manichaikul A, Foy M, Kabagambe EK, Nettleton JA, King IB, Weng LC, Bhattacharya S, Bandinelli S, Bis JC, Rich SS, Jacobs DR, Jr., Cherubini A, McKnight B, Liang S, Gu X, Rice K, Laurie CC, Lumley T, Browning BL, Psaty BM, Chen YD, Friedlander Y, Djousse L, Wu JH, Siscovick DS, Uitterlinden AG, Arnett DK, Ferrucci L, Fornage M, Tsai MY, Mozaffarian D, Steffen LM. Genetic Loci Associated with Plasma Phospholipid n-3 Fatty Acids: A Meta-Analysis of Genome-Wide Association Studies from the CHARGE Consortium. *PLoS Genet.* 2011;7:e1002193

E. Grants: none

Gene Expression

- A. Phenotypes: Whole Peripheral Blood Gene Expression: eQTLs and Differential Expression meta-analyses for age, gender and other traits
- B. Phenotypes actively being analyzed:
- C. WG Leaders: Andrew Johnson johnsonad2@nhlbi.nih.gov, Chris O'Donnell odonnellc@nhlbi.nih.gov, Marjolein Peters m.peters@erasmusmc.nl, Andre Uitterlinden a.g.uitterlinden@erasmusmc.nl, Joyce Van Meurs j.vanmeurs@erasmusmc.nl

- D. Publications

Westra et al. (2013) Systematic identification of trans eQTLs as putative drivers of known disease associations. Nat Gen, 45(10):1238-43.

Zhang et al. (2014) Synthesis of 53 tissue and cell line expression QTL datasets reveals master eQTLs. BMC Gen, 15:532.

Huan et al. (2015) A Meta-analysis of Gene Expression Signatures of Blood Pressure and Hypertension, PLoS Gen

Westra et al. (2015) Cell Specific eQTL Analysis without Sorting Cells. PLoS Genet. 2015 May; 11(5): e1005223.

- E. Grants: None

Gene-Lifestyle Interactions

A. Phenotypes: Blood Pressure (SBP, DBP, MAP, PP) Hypertension, Lipids (total cholesterol, triglycerides, HDL and LDL cholesterol)

B. Phenotypes actively being analyzed:

C. WG Leaders: DC Rao rao@wubios.wustl.edu, Ingrid Borecki iborecki@wustl.edu

D. Publications

Simino J, Sung YJ, Kume R, Schwander K, Rao DC. Gene-alcohol Interactions Identify Several Novel Blood Pressure Loci Including a Promising Locus Near SLC16A9. *Front Genet.* 2013 Dec 12;4:277.

Sung YJ, Schwander K, Arnett DK, Kardia SLR, Rankinen T, Bouchard C, Boerwinkle E, Hunt SC, Rao DC. An empirical comparison of meta-analysis and mega-analysis of individual participant data for identifying gene-environment interactions. *Genet Epidemiol.* 2014 May;38(4):369-78.

Basson JJ, Sung YJ, Schwander KL, Kume R, Simino J, de las Fuentes L, Rao DC. Gene-Education Interactions Identify Novel Blood Pressure Loci in the Framingham Heart Study. *Am J Hypertens.* 2014 Mar;27(3):431-44.

Sung YJ, de las Fuentes L, Schwander K, Simino J, Rao DC. Gene-smoking Interactions Identify Several Novel Blood Pressure Loci in the Family Heart Study. *Am J Hypertens.* 2014 Sep3. [Epub ahead of print]

Basson J, Sung YJ, de las Fuentes L, Schwander K, Cupples LA, Rao DC. Influence of Smoking Status and Intensity on Discovery of Blood Pressure Loci Through Gene-Smoking Interactions. *Genet Epidemiol.* 2015 May 3. Doi: 10.1002/gepi.21904. [Epub ahead of print]

E. Grants:

R01 HL107552 (Rao, PI) Gene-Environment Interactions in the Longitudinal Framingham Heart Study. 08/01/2011 - 03/31/2015. The primary goal of this study is to investigate gene-lifestyle interactions in cardiovascular traits in the Framingham longitudinal study data (SHARe). This study provided preliminary data for the large collaborative grant listed below and yielding a few preliminary publications.

R01 HL118305 (Rao, PI; Borecki, MPI) A Multi-Ethnic Study of Gene-Lifestyle Interactions in Cardiovascular Traits. 01/15/2014 – 12/31/2017: The primary goal is to investigate gene-lifestyle interactions, the genetic architecture of correlated traits with pleiotropy analysis, and pathway analysis, each as a means for uncovering more of the unexplained genetic variance in BP and lipids. We will do this by leveraging the extraordinary resources of existing multi-ethnic studies/cohorts that have the

phenotypes, relevant lifestyle data and dense genotype data on common (GWAS) as well as rare variants (Exome chip). This grant involves 51 study/race groups spanning 4 race/ethnic groups with GWAS and Exome chip data. Replication will be sought from two large consortia (Global BP Genetics or GBPgen, and Global Lipids Genetics Consortium or GLGC). This project involves an aggregate sample size over 300,000 in discovery/replication.

Glycemia/Diabetes

- A. Phenotypes: type 2 diabetes, hyperglycemia, insulin resistance, metabolic syndrome
- B. Phenotypes actively being analyzed: Fasting glucose, Fasting insulin, Fasting proinsulin, HbA1c, 2 hour OGTT glucose, 2 hour OGGT insulin, HOMA insulin resistance and beta cell function
- C. WG Leaders: James Meigs JMEIGS@mgh.harvard.edu, David Siscovick dsiscovick@nyam.org
- D. Publications

Variants in the melatonin receptor 1B gene (MTNR1B) influence fasting glucose levels.

New genetic loci implicated in fasting glucose homeostasis and their impact on type 2 diabetes risk.

Genetic variation in GIPR influences the glucose and insulin responses to an oral glucose challenge.

Common variants at ten genomic loci influence hemoglobin A1C levels via glycemic and non-glycemic pathways.

Genetic variants at 2q24 are associated with susceptibility to type 2 diabetes.

Twelve type 2 diabetes susceptibility loci identified through large-scale association analysis.

Detailed physiologic characterization reveals diverse mechanisms for novel genetic Loci regulating glucose and insulin metabolism in humans.

Racial/Ethnic Differences in Association of Fasting Glucose-Associated Genomic Loci with Fasting Glucose, HOMA-B and Impaired Fasting Glucose in U.S. Adult Population.

Interactions of dietary whole grain intake with fasting glucose- and insulin-related genetic loci in individuals of European descent: a meta-analysis of 14 cohort studies.

Meta-Analysis of Gene-Environment Interaction: Joint Estimation of SNP and SNP x Environment Regression Coefficients.

Genotype score in addition to common risk factors for prediction of type 2 diabetes.

Genetic risk reclassification for type 2 diabetes by age below or above 50 years using 40 type 2 diabetes risk single nucleotide polymorphisms.

Parental origin of sequence variants associated with complex diseases.

A genome-wide association study reveals variants in ARL15 that influence adiponectin levels.

Clear detection of ADIPOQ locus as the major gene for plasma adiponectin: Results of genome-wide association analyses including 4659 European individuals.

A genome-wide association study identifies a novel major locus for glycemic control in type 1 diabetes, as measured by both A1C and glucose.

Genetic evidence that raised sex hormone binding globulin (SHBG) levels reduce the risk of type 2 diabetes.

Variants in ACAD10 are associated with type 2 diabetes, insulin resistance and lipid oxidation in Pima Indians.

Variants at DGKB/TMEM195, ADRA2A, GLIS3 and C2CD4B loci are associated with reduced glucose-stimulated beta cell function in middle-aged Danish people.

Evaluating the discriminative power of multi-trait genetic risk scores for type 2 diabetes in a northern Swedish population.

Common inherited variation in mitochondrial genes is not enriched for associations with type 2 diabetes or related glycemic traits.

Genetic predisposition to long-term non-diabetic deteriorations in glucose homeostasis: ten-year follow-up of the GLACIER Study.

Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index.

Meta-analysis identifies 13 new loci associated with waist-hip ratio and reveals sexual dimorphism in the genetic basis of fat distribution.

Genetic Factors for Osteoporosis Consortium; Meta Analysis of Glucose and Insulin Related Traits Consortium.

Genome-wide association studies of serum magnesium, potassium, and sodium concentrations identify six Loci influencing serum magnesium levels.

Genome-Wide Association Study of Coronary Heart Disease and Its Risk Factors in 8,090 African Americans: The NHLBI CARe Project.

Genome-wide association analysis identifies variants associated with nonalcoholic fatty liver disease that have distinct effects on metabolic traits.

Association between parental history of diabetes and type 2 diabetes genetic risk scores in the PPP-Botnia and Framingham Offspring Studies.

Genome-wide association identifies nine common variants associated with fasting proinsulin levels and provides new insights into the pathophysiology of type 2 diabetes

Total Zinc Intake May Modify the Glucose-Raising Effect of a Zinc Transporter (SLC30A8) Variant: A 14-Cohort Meta-Analysis.

A Phenomics-Based Strategy Identifies Loci on APOC1, BRAP, and PLCG1 Associated with Metabolic Syndrome Phenotype Domains.

Common genetic variants differentially influence the transition from clinically defined states of fasting glucose metabolism. (CARe collaboration)

Large-Scale Gene-Centric Meta-Analysis across 39 studies Identifies Type 2 Diabetes Loci. (CARe collaboration)

A genome-wide association search for type 2 diabetes genes in African Americans. (AAGILE-MAGIC-MEDIA collaboration)

No Interactions between Previously Associated 2-h Glucose Gene Variants and Physical Activity or BMI on 2-h Glucose Levels.

Novel Loci for adiponectin levels and their influence on type 2 diabetes and metabolic traits: a multi-ethnic meta-analysis of 45,891 individuals.

Discovery of genetic variants implicated in insulin resistance through novel application of a genome-wide approach that accounts for body mass index and SNP by body mass index interaction on fasting glycemic traits.

Fasting Glucose GWAS Candidate Region Analysis Across Ethnic Groups in the Multiethnic Study of Atherosclerosis (MESA).

Race-ethnic differences in the association of genetic loci with HbA1C levels and mortality in U.S. adults: the third National Health and Nutrition Examination Survey (NHANES III).

Stratifying Type 2 Diabetes Cases by BMI Identifies Genetic Risk Variants in LAMA1 and Enrichment for Risk Variants in Lean Compared to Obese Cases.

Impact of Common Variation in Bone-Related Genes on Type 2 Diabetes and Related Traits.

A genotype risk score predicts type 2 diabetes from young adulthood: the CARDIA study.

Large-scale association analysis provides insights into the genetic architecture and pathophysiology of type 2 diabetes.

Large-scale association analyses identify new loci influencing glycemic traits and provide insight into the underlying biological pathways.

Transferability and fine-mapping of glucose and insulin quantitative trait loci across populations: CARe, the Candidate Gene Association Resource.

Genome-wide association study for circulating levels of plasminogen activator inhibitor-1 (PAI-1) provides novel insights into the regulation of PAI-1.

Genotype prediction of adult type 2 diabetes from adolescence in a multiracial population.

Transferability and Fine Mapping of Type 2 Diabetes Loci in African Americans: The Candidate Gene Association Resource Plus Study.

Meta-Analysis Investigating Associations Between Healthy Diet and Fasting Glucose and Insulin Levels and Modification by Loci Associated With Glucose Homeostasis in Data From 15 Cohorts.

Sequence Kernel Association Test for Quantitative Traits in Family Samples.

Higher Magnesium Intake Is Associated with Lower Fasting Glucose and Insulin, with No Evidence of Interaction with Select Genetic Loci, in a Meta-Analysis of 15 CHARGE Consortium Studies.

Lack of interaction of beta-cell-function-associated variants with hypertension on change in fasting glucose and diabetes risk: the Framingham Offspring Study.

Common variants in and near IRS1 and subclinical cardiovascular disease in the Framingham Heart Study.

Mendelian randomization studies do not support a causal role for reduced circulating adiponectin levels in insulin resistance and type 2 diabetes.

Assessing the phenotypic effects in the general population of rare variants in genes for a dominant Mendelian form of diabetes.

Incorporating gene-environment interaction in testing for association with rare genetic variants.

Magnesium intake is inversely associated with coronary artery calcification: the Framingham Heart Study.

Impact of type 2 diabetes susceptibility variants on quantitative glycemic traits reveals mechanistic heterogeneity.

Genome-wide trans-ancestry meta-analysis provides insight into the genetic architecture of type 2 diabetes susceptibility.

Polygenic type 2 diabetes prediction at the limit of common variant detection.

Association of Levels of Fasting Glucose and Insulin with Rare Variants at the Chromosome 11p11.2-MADD Locus: the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Targeted Sequencing Study.

Pleiotropic genes for metabolic syndrome and inflammation.

Incorporating gene-environment interaction in testing for association with rare genetic variants.

Identification of a novel gene for diabetic traits in rats, mice, and humans

Low-frequency and rare exome chip variants associate with fasting glucose and type 2 diabetes susceptibility.

Association of a 62 Variant Type 2 Diabetes Genetic Risk Score with Markers of Subclinical Atherosclerosis: A Transethnic, Multicenter Study.

E. Grants:

2 R01 DK078616-05 (Meigs) Common Genetic Variation and Diabetes Quantitative Traits. The goal of this competing continuation is to discover genes associated with type 2 diabetes-related quantitative traits (fasting glucose, insulin and HbA1c) in a large (N~103,000) trans-ethnic (African American, European, Hispanic and Asian) consortium sample, then test high interest variants in physiology, interaction and population prediction studies in trans-ethnic longitudinal Studies. FHS SHARe, CHS, ARIC, MESA, CARDIA and other CHARGE cohorts are included in this grant.

1 U01 DK085526 (Altshuler, Meigs, Jablonski, Wilson) Multiethnic Study of Type 2 Diabetes Genetics. The goal is to define variation within type 2 diabetes risk genes by bringing together - 29,000 individuals from ethnic groups representing the US population, map genes in each region, and identify mutations by detailed DNA analysis, leading to better prevention and treatment.

American Diabetes Association (Meigs) Genetics of Type 2 Diabetes Quantitative Traits. The goal is to support a post-doctoral research fellow to train in a clinical research environment committed to identification of novel approaches for prevention of type 2 diabetes.

2 R01 DK078616-08 Rare Genetic Variation and Diabetes Quantitative Traits (Meigs). The goal is to identify type 2 diabetes-quantitative trait-associated functional rare variants using whole genome sequence scans in ~3,700 white and black individuals from three cohorts in the CHARGE (Cohorts for Heart and Aging Research in Genomic Epidemiology) consortium. We will phenotype associated variants with existing physiological data in CHARGE, including tests for T2D risk, annotate variants using ENCODE and other resources, and confirm predicted allele-specific molecular function in vitro with appropriate experiments in appropriate cells in order to generate new molecular hypotheses that advance translation of genetics into better T2D prevention and care

Hearing loss

- A. Phenotypes: Age-related hearing loss
- B. Phenotypes actively being analyzed:
- C. WG Leaders: Paul Nagtegaal a.nagtegaal@erasmusmc.nl, Andre Goedegebure a.goedegebure@erasmusmc.nl
- D. Publications: none
- E. Grants: no information available at this time

Heart Failure

- A. Phenotypes: Incident heart failure, heart failure mortality
- B. Phenotypes actively being analyzed: incident HF and HF mortality
- C. WG Leaders: Nick Smith nlsmith@u.washington.edu, Vasan Ramachandran vasan@bu.edu
- D. Publications:

Association of genome-wide variation with the risk of incident heart failure in adults of European and African ancestry: a prospective meta-analysis from the cohorts for heart and aging research in genomic epidemiology (CHARGE) consortium. Smith NL, Felix JF, Morrison AC, Demissie S, Glazer NL, Loehr LR, Cupples LA, Dehghan A, Lumley T, Rosamond WD, Lieb W, Rivadeneira F, Bis JC, Folsom AR, Benjamin E, Aulchenko YS, Haritunians T, Couper D, Murabito J, Wang YA, Stricker BH, Gottdiener JS, Chang PP, Wang TJ, Rice KM, Hofman A, Heckbert SR, Fox ER, O'Donnell CJ, Uitterlinden AG, Rotter JI, Willerson JT, Levy D, van Duijn CM, Psaty BM, Wittman JC, Boerwinkle E, Vasan RS. Circ Cardiovasc Genet. 2010 Jun 1;3(3):256-66. PMID: 20445134

Genomic variation associated with mortality among adults of European and African ancestry with heart failure: the cohorts for heart and aging research in genomic epidemiology consortium. Morrison AC, Felix JF, Cupples LA, Glazer NL, Loehr LR, Dehghan A, Demissie S, Bis JC, Rosamond WD, Aulchenko YS, Wang YA, Haritunians T, Folsom AR, Rivadeneira F, Benjamin EJ, Lumley T, Couper D, Stricker BH, O'Donnell CJ, Rice KM, Chang PP, Hofman A, Levy D, Rotter JI, Fox ER, Uitterlinden AG, Wang TJ, Psaty BM, Willerson JT, van Duijn CM, Boerwinkle E, Wittman JC, Vasan RS, Smith NL. Circ Cardiovasc Genet. 2010 Jun 1;3(3):248-55. PMID: 20400778

- E. Grants: none

Hematology

- A. Phenotypes: Red blood cell and white blood cell traits
- B. Phenotypes actively being analyzed:
- C. WG Leaders: Santhi Ganesh sganesh@med.umich.edu, Chris O'Donnell odonnellc@nhlbi.nih.gov
- D. Publications:

Multiple loci influence erythrocyte phenotypes in the CHARGE consortium. *Nature Genetics*. 2009

Multiple loci are associated with white blood cell phenotypes. *PLoS Genetics*. 2011

Genome-wide association study of white blood cell count in 16,388 African Americans: the continental origins and genetic epidemiology network (COGENT). *PLoS Genetics*. 2011

Identification of nine novel loci associated with white blood cell subtypes in a Japanese population. *PLoS Genetics*. 2011

New gene functions in megakaryopoiesis and platelet formation. *Nature* 2011. (in collaboration with the CHARGE Hemostasis Working Group).

Genome-wide association study of mild retinopathy in individuals without diabetes and hypertension identifies a novel locus associated with kidney disease (collaboration with the Retinopathy WG), *PLoS One* 2013.

Genetic variation associated with circulating monocyte count in the eMERGE Network. *Human Molecular Genetics* 2013

Genetic Associations with Expression for Genes Implicated in GWAS Studies for Atherosclerotic Cardiovascular Disease and Blood Phenotypes. *Hum Mol Genet*. 2013

Genome wide association analysis of a founder population identified TAF3 as a gene for MCHC in humans. *PloS One*. 2013

Multiple Non-glycemic Genomic Loci Are Newly Associated with Blood Level of Glycated Hemoglobin in East Asians. *Diabetes*. 2014

Pleiotropic genes for metabolic syndrome and inflammation. *Mol Genet Metab*. 2014

Trans-ethnic fine-mapping of white blood cell genetic associations. *Human Molecular Genetics*. 2014.

- E. Grants: none

Hemostasis

A. Phenotypes: Fibrinogen, factor VII, factor VIII, von Willebrand factor, platelet count, D-dimer, PAI-1, tPA

B. Phenotypes actively being analyzed: Fibrinogen, FVII, FVIII, and vWF

C. WG Leaders: Nick Smith nlsmith@u.washington.edu, Chris O'Donnell odonnellc@nhlbi.nih.gov

D. Publications:

Dehghan A, Yang Q, Peters A, [...], Strachan DP, Smith NL, Folsom AR. Association of Novel Genetic Loci with Circulating Fibrinogen Levels: A Genome-Wide Association Study in Six Population-Based Cohorts. *Circ Cardiovasc Genet* 2009;2:125-133. (PMC2764985)

Smith NL, Chen M, Dehghan A, [...], Witteman JC, Tang W, O'Donnell JC. Novel associations of multiple genetic loci with plasma levels of factor VII, factor VIII, and von Willebrand factor: The CHARGE Consortium. *Circulation* 2010;121:1382-92. (PMC2861278)

van Loon JE, Leebeek FW, Deckers JW, [...], O'Donnell CJ, Smith NL, de Maat MP. Effect of genetic variations in syntaxin-binding protein-5 and syntaxin-2 on von Willebrand factor concentration and cardiovascular risk. *Circ Cardiovasc Genet* 2010;3:507-12. (PMC3511837)

Smith NL, Huffman JE, Strachan DP, [...], Soranzo N, Koenig W, Hayward C. Genetic predictors of fibrin D-dimer levels in healthy adults. *Circulation* 2011;123:1864-72. (PMC3095913)

Huang J, Sabater-Lleal M, Asselbergs FW, [...] Liu Y, O'Donnell CJ, Hamsten A. Genome-wide association study for circulating levels of plasminogen activator inhibitor-1 (PAI-1) provides novel insights into the regulation of PAI-1. *Blood* 2012. (PMC35206240)

Tang W, Schwienbacher C, Lopez LM, [...], Deary IJ, Hicks AA, Folsom AR. Genetic associations for activated partial thromboplastin time and prothrombin time, their gene expression profiles, and risk of coronary artery disease. *Am J Hum Genet.* 2012;91:152-62. (PMC3397273)

Sabater-Lleal M, Huang J, Chasman D, Naitza S, Dehghan A, Johnson AD, [...], Smith NL, Tregouet D, Ridker PM, Tang W, Strachan DP, Hamsten A, O'Donnell CJ. Multiethnic meta-analysis of genome-wide association studies in >100 000 subjects identifies 23 fibrinogen-associated Loci but no strong evidence of a causal association between circulating fibrinogen and cardiovascular disease. *Circulation.* 2013;128(12):1310-24. (PMC3842025)

Huang J, Huffman JE, Yamakuchi M, [...], Lowenstein CJ, Strachan DP, O'Donnell CJ; CHARGE Consortium Hemostatic Factor Working Group. Genome-wide association study for circulating tissue plasminogen activator levels and functional follow-up implicates endothelial STXBP5 and STX2. Arterioscler Thromb Vasc Biol. 2014;34:1093-101.

Baumert J, Huang J, McKnight B, [...], Strachan DP, Peters A, Smith NL. No evidence for genome-wide interactions on plasma fibrinogen by smoking, alcohol consumption and body mass index: results from meta-analyses of 80,607 subjects. PLoS One. 2014;9:e111156.

E. Grants: none pending

Inflammation

A. Phenotypes: Inflammatory associated biomarkers and traits

B. Phenotypes actively being analyzed:

C. WG Leaders: Behrooz Z. Alizadeh b.z.alizadeh@umg.nl

D. Publications:

Association of Novel Genetic Loci with Circulating Fibrinogen Levels: A Genome-Wide Association Study in Six Population-Based Cohorts. Abbas Dehghan et al. *Circ Cardiovasc Genet.* 2009 2:125–133.

Meta-analysis of genome-wide association studies in >80,000 subjects identifies multiple loci for C-reactive protein levels. Abbas Dehghan et al. *Circulation.* 2011 22; 123: 731–738.

Eight genetic loci associated with variation in lipoprotein-associated phospholipase A2 mass and activity and coronary heart disease: meta-analysis of genome-wide association studies from five community-based studies. Harald Grallert et al, *Eur Heart J.* 2012 33:238-51.

Genome-wide and gene-centric analyses of circulating myeloperoxidase levels in the charge and care consortia. Reiner AP et al. *Hum Mol Genet.* 2013 2013 15;22:3381-93.

Mining the human phenotype using allelic scores that index biological intermediates. Evans DM, Brion MJ, Paternoster L, Kemp JP, McMahon G, Munafò M, Whitfield JB, Medland SE, Montgomery GW; GIANT Consortium; CRP Consortium; TAG Consortium, Timpson NJ, St Pourcain B, Lawlor DA, Martin NG, Dehghan A, Hirschhorn J, Davey Smith G.

PLOS Gentic 2013; 9:e1003919. doi: 10.1371/journal.pgen.1003919. Epub 2013 Oct 31.

QCGWAS: A flexible R package for automated quality control of genome-wide association results. 5. van der Most PJ, Vaez A, Prins BP, Munoz ML, Snieder H, Alizadeh BZ, Nolte IM. *Bioinformatics.* 2014 Jan

E. Grants: none

Insulin Like Growth Factor

- A. Phenotypes: Circulating levels of IGF-I, IGFBP-3, and related proteins
- B. Phenotypes actively being analyzed:
- C. WG Leaders: Robert Kaplan Robert.Kaplan@einstein.yu.edu, Vasan Ramachandran vasan@bu.edu

D. Publications:

Kaplan et al. A genome-wide association study identifies novel loci associated with circulating IGF-I and IGFBP-3. Human Molecular Genetics 2011

Wang T, Zhou B, Guo T, Bidlingmaier M, Wallaschofski H, Teumer A, Vasan RS, Kaplan RC. A robust method for genome-wide association meta-analysis with the application to circulating insulin-like growth factor I concentrations. Genet Epidemiol. 2014 Feb;38(2):162-71. doi: 10.1002/gepi.21766. Epub 2013 Oct 25.

Evans DS, Cailotto F, Parimi N, Valdes AM, Castaño-Betancourt MC, Liu Y, Kaplan RC, Bidlingmaier M, Vasan RS, Teumer A, Tranah GJ, Nevitt MC, Cummings SR, Orwoll ES, Barrett-Connor E, Renner JB, Jordan JM, Doherty M, Doherty SA, Uitterlinden AG, van Meurs JB, Spector TD, Lories RJ, Lane NE. Genome-wide association and functional studies identify a role for IGFBP3 in hip osteoarthritis Ann Rheum Dis. 2014 Jun 13. pii: annrheumdis-2013-205020. doi: 10.1136/annrheumdis-2013-205020. PMID: 24928840 PMID: 24446417

E. Grants: none

Lipids

- A. Phenotypes: low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, total cholesterol, NMR lipoprotein phenotypes, plasma apoB, plasma apoAI, plasma Lp(a)
- B. Phenotypes actively being analyzed:
- C. WG Leaders: Adrienne Cupples adrienne@bu.edu, Gina Peloso gina@broadinstitute.org, Sekar Kathiresan sekar@broad.mit.edu, Josh Bis joshbis@u.washington.edu, Eric Boerwinkle Eric.Boerwinkle@uth.tmc.edu, Jerry Rotter jrotter@labiomed.org

D. Publications:

van Leeuwen EM, et al. Population-specific imputations identify a ABCA6 variant associated with cholesterol levels: the Genome of the Netherlands. *Nat Commun.* 2015 Mar 9;6:6065.

Peloso GM, et al. Association of low-frequency and rare protein-coding sequence variants with blood lipids in 56,000 individuals of European and African-American ancestries. *Am J Hum Genet.* 2014 Feb 6;94(2):223-32.

Lange LA, et al. Novel rare and low frequency coding variants associated with LDL cholesterol. *Am J Hum Genet.* 2014 Feb 6;94(2):233-45.

Global Lipids Genetics Consortium, Willer CJ, Schmidt EM, Sengupta S, Peloso GM, Gustafsson S, Kanoni S, Ganna A, et al. Discovery and refinement of loci associated with lipid levels. *Nat Genet* 2013 Nov;45(11):1274-83.

Do R, Willer CJ, Schmidt EM, Sengupta S, Gao C, Peloso GM, Gustafsson S, Kanoni S, Ganna A, et al. Common variants associated with plasma triglycerides and risk for coronary artery disease. *Nat Genet* 2013 Nov;45(11):1345-52.

Teslovich TM*, Musunuru K*, Global Lipids Genetics Consortium Collaborators, Cupples LA*, Sandhu MS*, Ridker PM*, Rader DJ*, van Duijn CM*, Peltonen L*, Abecasis GR*, Boehnke M*, Kathiresan S*. Biological, clinical, and population relevance of 95 loci for blood lipids. *Nature* 2010;466: 707-713.

Kathiresan S*, Willer C*, Peloso G*, Demissie S*, ... Jose M Ordovas*, Michael Boehnke*, Goncalo R Abecasis*, Karen L Mohlke* & L Adrienne Cupples* Common DNA sequence variants at thirty genetic loci contribute to polygenic dyslipidemia. *Nat Genet* 2009;41: 56-65.

E. Grants: none

Microbiome

- A. Phenotypes: Gut microbiome compositions by means of 16S rRNA sequencing and shotgun metagenomic sequencing; H. pylori status
- B. Phenotypes actively being analyzed:
- C. WG Leaders: Robert Kraaij r.kraaij@erasmusmc.nl
- D. Publications: none
- E. Grants: none

Musculoskeletal

A. Phenotypes: Bone mineral density by DXA, lean mass by DXA and/or bioimpedance analysis, hip geometry by DXA, calcaneal quantitative ultrasound, bone mineral density and geometry by QCT, bone mineral density and bone microarchitecture by high resolution peripheral quantitative computed tomography (HR-pQCT), vertebral fracture, hip fracture, sarcopenic obesity, serum osteocalcin, serum osteoprotegerin, and grip and lower extremity strength.

B. Phenotypes actively being analyzed:

C. WG Leaders: Doug Kiel kiel@hsl.harvard.edu, Andre Uitterlinden a.g.uitterlinden@erasmusmc.nl, Fernando Rivadeneira f.rivadeneira@erasmusmc.nl

D. Publications:

Rivadeneira F*, Styrkársdóttir U*, Estrada K*, Halldorsson B*, Hsu YH*, Richards JB*, Zillikens MC*, Kavvoura FK*, Amin N, Aulchenko YA, Cupples LA, Deloukas P, Demissie S, Grundberg E, Hofman A, Kong A, Karasik D, van Meurs JM, Oostra B, Pastinen T, Pols HAP, Sigurdsson G, Soranzo N, Thorleifsson G, Thorsteinsdottir U, Williams FMK, Wilson SG, Zhou Y, Ralston S, van Duijn CM, Spector T*, Kiel DP*, Stefansson K*, Ioannidis JPA*, Uitterlinden AG* for the GEnetic Factors For Osteoporosis (GEFOS) Consortium. Twelve novel loci associated with bone mineral density identified by large-scale meta-analysis of genome-wide association datasets. *Nature Genetics*, 2009;41:1199-1206.

Richards JB, Kavvoura FK, Rivadeneira F, Styrkársdóttir U, Estrada K, Halldórsson BV, Hsu YH, Zillikens MC, Wilson SG, Mullins BH, Amin N, Aulchenko YS, Cupples LA, Deloukas P, Demissie S, Hofman A, Kong A, Karasik D, van Meurs JB, Oostra BA, Pols HAP, Sigurdsson G, Thorsteinsdottir U, Soranzo N, Williams FMK, Zhou Y, Ralston SH, Thorleifsson G, van Duijn CM, Kiel DP, Stefansson K, Uitterlinden AG, Ioannidis JPA, Spector TD for the GEnetic Factors For Osteoporosis (GEFOS) Consortium. A systematic evaluation of 147 candidate genes for their association with osteoporosis and osteoporotic fracture in a meta-analysis of genome-wide association data. *Ann Int Med* 2009; 151:528-37.

Hsu YH, Zillikens MC, Wilson SG, Farber CR, Demissie S, Soranzo N, Bianchi EN, Grundberg E, Liang L, Richards JB, Estrada K, Zhou Y, van Nas A, Moffatt MF, Zhai G, Hofman A, van Meurs JB, Pols HA, Price RI, Nilsson O, Pastinen T, Cupples LA, Lusis AJ, Schadt EE, Ferrari S, Uitterlinden AG, Rivadeneira F, Spector TD, Karasik D, Kiel DP. An integration of genome-wide association study and gene expression profiling to prioritize the discovery of novel susceptibility Loci for osteoporosis-related traits. *PLoS Genet*. 2010 June; 6(6): e1000977

Kung AW, Xiao SM, Cherny S, Li GH, Gao Y, Tso G, Lau KS, Luk KD, Liu JM, Cui B, Zhang MJ, Zhang ZL, He JW, Yue H, Xia WB, Luo LM, He SL, Kiel DP, Karasik D, Hsu YH, Cupples LA, Demissie S, Styrkarsdottir U, Halldorsson BV, Sigurdsson G, Thorsteinsdottir U, Stefansson K, Richards JB, Zhai G, Soranzo N, Valdes A, Spector TD, Sham PC. Association of JAG1 with bone mineral density and

osteoporotic fractures: A genome-wide association study and follow-up replication studies. Am J Hum Genet. 2010;86:229-239.

Billings LK, Hsu YH, Ackerman RJ, Dupuis J, Voight BF, Rasmussen-Torvik LJ, Hercberg S, Lathrop M, Barnes D, Langenberg C, Hui J, Fu M, Bouatia-Naji N, Lecoeur C, An P, Magnusson PK, Surakka I, Ripatti S, Christiansen L, Dalgård C, Folkersen L, Grundberg E; MAGIC Investigators; DIAGRAM + Consortium; MuTHER Consortium; ASCOT Investigators; GEFOS Consortium, Eriksson P, Kaprio J, Ohm Kyvik K, Pedersen NL, Borecki IB, Province MA, Balkau B, Froguel P, Shuldiner AR, Palmer LJ, Wareham N, Meneton P, Johnson T, Pankow JS, Karasik D, Meigs JB, Kiel DP, Florez JC. Impact on common variation in bone-related genes on type 2 diabetes and related traits. Diabetes. 2012 Aug;61(8):2176-86.

Estrada K, Styrkarsdottir U, Evangelou E, Hsu YH, Duncan EL, Ntzani EE, Oei L, Albagha OM, Amin N, Kemp JP, Koller DL, Li G, Liu CT, Minster RL, Moayyeri A, Vandenput L, Willner D, Xiao SM, Yerges-Armstrong LM, Zheng HF, Alonso N, Eriksson J, Kammerer CM, Kaptoge SK, Leo PJ, Thorleifsson G, Wilson SG, Wilson JF, Aalto V, Alen M, Aragaki AK, Aspelund T, Center JR, Dailiana Z, Duggan DJ, Garcia M, Garcia-Giralt N, Giroux S, Hallmans G, Hocking LJ, Husted LB, Jameson KA, Khusainova R, Kim GS, Kooperberg C, Koromila T, Kruk M, Laaksonen M, Lacroix AZ, Lee SH, Leung PC, Lewis JR, Masi L, Mencej-Bedrac S, Nguyen TV, Nogues X, Patel MS, Prezelj J, Rose LM, Scollen S, Siggeirsottir K, Smith AV, Svensson O, Trompet S, Trummer O, van Schoor NM, Woo J, Zhu K, Balcells S, Brandi ML, Buckley BM, Cheng S, Christiansen C, Cooper C, Dedoussis G, Ford I, Frost M, Goltzman D, González-Macías J, Kähönen M, Karlsson M, Khusnutdinova E, Koh JM, Kollia P, Langdahl BL, Leslie WD, Lips P, Ljunggren O, Lorenc RS, Marc J, Mellström D, Obermayer-Pietsch B, Olmos JM, Pettersson-Kymmer U, Reid DM, Riancho JA, Ridker PM, Rousseau F, Lagboom PE, Tang NL, Urreizti R, Van Hul W, Viikari J, Zarzabeitia MT, Aulchenko YS, Castano-Betancourt M, Grundberg E, Herrera L, Ingvarsson T, Johannsdottir H, Kwan T, Li R, Luben R, Medina-Gómez C, Th Palsson S, Reppe S, Rotter JI, Sigurdsson G, van Meurs JB, Verlaan D, Williams FM, Wood AR, Zhou Y, Gautvik KM, Pastinen T, Raychaudhuri S, Cauley JA, Chasman DI, Clark GR, Cummings SR, Danoy P, Dennison EM, Eastell R, Eisman JA, Gudnason V, Hofman A, Jackson RD, Jones G, Jukema JW, Khaw KT, Lehtimäki T, Liu Y, Lorentzon M, McCloskey E, Mitchell BD, Nandakumar K, Nicholson GC, Oostra BA, Peacock M, Pols HA, Prince RL, Raitakari O, Reid IR, Robbins J, Sambrook PN, Sham PC, Shuldiner AR, Tylavsky FA, van Duijn CM, Wareham NJ, Cupples LA, Econs MJ, Evans DM, Harris TB, Kung AW, Psaty BM, Reeve J, Spector TD, Streeten EA, Zillikens MC, Thorsteinsdottir U, Ohlsson C, Karasik D, Richards JB, Brown MA, Stefansson K, Uitterlinden AG, Ralston SH, Ioannidis JP, Kiel DP, Rivadeneira F. Genome-wide meta-analysis identifies 56 bone mineral density loci and reveals 14 loci associated with risk of fracture. Nat Genet. 2012 Apr 15;44(5):491-501.

Zheng HF, Tobias JH, Duncan E, Evans DM, Eriksson J, Paternoster L, Yerges-Armstrong LM, Lehtimäki T, Bergström U, Kähönen M, Leo PJ, Raitakari O, Laaksonen M, Nicholson GC, Viikari J, Ladouceur M,

Lytykäinen LP, Medina-Gomez C, Rivadeneira F, Prince RL, Sievanen H, Leslie WD, Mellström D, Eisman JA, Movérare-Skrtic S, Goltzman D, Hanley DA, Jones G, St Pourcain B, Xiao Y, Timpson NJ, Smith GD, Reid IR, Ring SM, Sambrook PN, Karlsson M, Dennison EM, Kemp JP, Danoy P, Sayers A, Wilson SG, Nethander M, McCloskey E, Vandenput L, Eastell R, Liu J, Spector T, Mitchell BD, Streeten EA, Brommage R, Pettersson-Kymmer U, Brown MA, Ohlsson C, Richards JB, Lorentzon M., WNT16 influences bone mineral density, cortical bone thickness, bone strength, and osteoporotic fracture risk. *PLoS Genet.* 2012 Jul;8(7):e1002745.

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Koller DL, Zheng HF, Karasik D, Yerges-Armstrong L, Liu CT, McGuigan F, Kemp JP, Giroux S, Lai D, Edenberg HJ, Peacock M, Czerwinski SA, Choh AC, McMahon G, St Pourcain B, Timpson NJ, Lawlor DA, Evans DM, Towne B, Blangero J, Carless MA, Kammerer C, Goltzman D, Kovacs CS, Prior JC, Spector TD, Rousseau F, Tobias JH, Akesson K, Econo MJ, Mitchell BD, Richards JB, Kiel DP, Foroud T. Meta-analysis of genome-wide studies identifies WNT16 and ESR1 SNPs associated with bone mineral

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E. Grants:

Kiel, DP and Glimcher, L. Supplement to existing NIAMS R01 AR 41398, "Building Interdisciplinary Research Teams" Dates: 7/1/10 – 6/30/11

Kiel DP. NIAMS R01 AR061162 "Targeted Sequencing of 3 Loci Associated with BMD in the

Framingham Osteoporosis Study.Dates: 5/1/11-4/30/14

Karasik, David. NIAMS R01 AR057118 Unraveling Musculoskeletal Pleiotropy Using Genome-Wide Association Dates: 7/1/09- 6/31/11

Hsu, Yi-Hsiang, NIAMS R21 AR056405 "Osteocalcin and Metabolic Risk Factors. A Genome-Wide Association Study in Framingham Cohorts" Dates: 7/1/10 – 6/30/13

Karasik, David. Glenn Foundation Award in Biology Of Aging (unsolicited contribution) Dates: 2011 - 2012

Kiel DP. NIAMS R01 AR 061445 "Bone Microarchitecture: The Framingham Osteoporosis." Dates: 5/1/12 - 4/30/17

Rivadeneira, Fernando 2013-2018 VIDI-016.136.367 Netherlands Organization for Scientific Research (NWO), "From genetic discoveries to clinical applications: comprehensive phenotyping of the musculoskeletal system"

Natriuretic Peptides

- A. Phenotypes:
- B. Phenotypes actively being analyzed:
- C. WG Leaders: Thomas Wang TJWANG@mgh.harvard.edu, Dan Levy levyd@nhlbi.nih.gov
- D. Publications: none
- E. Grants: none

Neurology (specific subgroups on Stroke, Dementia, Cognitive Function, Brain MRI)

- A. Phenotypes: Stroke (total, ischemic [large artery atherothrombotic, lacune, cardioembolic] hemorrhagic, incident stroke), Dementia (All, Alzheimer's disease (including incident), vascular dementia), Cognitive function tests (global cognition and domain specific including the domains of verbal memory, processing speed, fluency, executive function, verbal learning/immediate recall, vocabulary, visuospatial function, finger tapping; also change in cognitive function across these domains), Cognitive reserve. Healthy Brain Aging, Measures derived from brain MRI, total intracranial and cerebral volumes, hippocampal volumes, ventricular volumes, lobar volumes (frontal, temporal, parietal, occipital), and regional and total gray and white matter volumes, deep subcortical structures, MRI brain infarcts (and lacunes/cerebral small vessel disease), WMH, DTI global and regional ROIs in tracts, cerebral microbleeds, progression in WMH. Vertical pleiotropy analyses across these phenotypes. GEWAS (TCBV/alcohol, WMH/HTN, WMH/sex). Mendelian randomization and risk prediction approaches (using outcome specific and risk factor specific approaches).
- B. Phenotypes underlined have abstracts/papers re-submitted or under review.
- C. Phenotypes actively being analyzed:
- D. WG Leader: Sudha Seshadri suseshad@bu.edu
- E. Publications:

Broer L, Buchman AS, Deelen J, et al. GWAS of longevity in CHARGE consortium confirms APOE and FOXO3 candidacy. *The journals of gerontology Series A, Biological sciences and medical sciences* 2015;70:110-8.

Chauhan G, Adams HH, Bis JC, et al. Association of Alzheimer's disease GWAS loci with MRI markers of brain aging. *Neurobiology of aging* 2015.

Chouraki V, Beiser A, Younkin L, et al. Plasma amyloid-beta and risk of Alzheimer's disease in the Framingham Heart Study. *Alzheimer's & dementia : the journal of the Alzheimer's Association* 2015;11:249-57 e1.

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Lopez LM, Hill WD, Harris SE, et al. Genes from a translational analysis support a multifactorial nature of white matter hyperintensities. *Stroke; a journal of cerebral circulation* 2015;46:341-7.

Rannikmae K, Davies G, Thomson PA, et al. Common variation in COL4A1/COL4A2 is associated with sporadic cerebral small vessel disease. *Neurology* 2015;84:918-26.

van der Lee SJ, Holstege H, Wong TH, et al. PLD3 variants in population studies. *Nature* 2015;520:E2-E3.

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Escott-Price V, Bellenguez C, Wang LS, et al. Gene-wide analysis detects two new susceptibility genes for Alzheimer's disease. *PLoS one* 2014;9:e94661.

F. Grants:

AGES: NIA contract N01-AG-12100 with contributions from NEI, NIDCD and NHLBI, the NIA Intramural Research Program, Hjartavernd (the Icelandic Heart Association), and the Althingi (the Icelandic Parliament).

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Erasmus Rucphen Family Study: We thank the participants from the Genetic Research in Isolated Populations in the Erasmus Rucphen Family Study who made this work possible. This study is financially supported by the Netherlands Organisation for Scientific Research (NWO), the Internationale Stichting Alzheimer Onderzoek (ISAO), the Hersenstichting Nederland (HSN) and the Centre for Medical Systems Biology (CMSB1 and CMSB2) in the framework of the Netherlands Genomics Initiative (NGI).

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Nutrition

- A. Phenotypes: Our working group interacts with other phenotype working groups to characterize diet-gene interaction, as well as pursues independent research of the genetic predictors of dietary intake. To encourage collaboration and minimize problems with project overlap, our protocol is to first contact the phenotype working group most closely related to the outcome of interest. Similarly, we encourage phenotype working groups to contact us regarding plans to study interactions between genotype and dietary intake. Phenotypes underlined have abstracts/papers re-submitted or under review.
- B. Phenotypes actively being analyzed: Main Effects (GWAS): Macronutrient intake, Fish intake, EPA+DHA intake, Coffee intake, Plasma Vitamin K; Interaction (GWI or candidate gene): Gene-dairy interaction on BMI, fasting glucose and fasting insulin, Gene-macronutrient intake on sleep duration, Gene-sleep duration interaction on dietary intake, Gene-macronutrient on lipid levels (HDL-C, LDL-C, TG), Gene-Mg/Zn/Whole grains on fasting glucose and fasting insulin, Gene-PUFA intake on lipid levels (HDL-C, LDL-C, TG)
- C. WG Leaders: Caren Smith caren.smith@tufts.edu, Tosh Tanaka tanakato@mail.nih.gov
- D. Publications:

Interactions of dietary whole grain intake with fasting glucose- and insulin-related genetic loci in individuals of European descent: a meta-analysis of 14 cohort studies. *Diabetes Care*, 33:2684-2691, 2010. PMCID: PMC2992213 JA Nettleton, NM McKeown, S Kanoni, RN Lemaitre, MF Hivert, J Ngwa, FJA van Rooij, E Sonestedt, MK Wojczynski, Z Ye, T Tanaka, M Garcia, JS Anderson, JL Follis, L Djousse, K Mukamal, C Papoutsakis, D Mozaffarian, C Zillikens, S Bandinelli, AJ Bennett, IB Borecki, MF Feitosa, L Ferrucci, NG Forouhi, CJ Groves, G Hallmans, T Harris, A Hofman, DK Houston, FB Hu, I Johansson, SB Kritchevsky, C Langenberg, L Launer, Y Liu, RJ Loos, M Nalls, M Orho-Melander, F Renstrom, K Rice, U Riserus, O Rolandsson, JI Rotter, GSaylor, EJG Sijbrands, P Sjogren, ASmith, L Steingrimsdóttir, AG Uitterlinden, NJ Wareham, I Prokopenko, JS Pankow, CM van Duijn, JC Florez, JCM Wittemanthe MAGIC Investigators, JDupuis, George V Dedoussis, JM Ordovas, E Ingelsson, LA Cupples, DS Siscovick, PW Franks, JB Meigs.

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Dupuis, C Langenberg, L Ferrucci, SB Kritchevsky, E Ingelsson, IB Borecki, JCM Witteman, M Orho-Melander, DS Siscovick, JB Meigs, PW Franks, GV Dedoussis.

Meta-analyses of 15 cohorts show inverse associations between healthy diet and fasting glucose and insulin and no evidence of modification by multiple loci associated with glucose homeostasis. Am J Epidemiol, 177(2):103-105. PMID: 23255780 JA Nettleton, MF Hivert, RN Lemaitre, NM McKeown, D Mozaffarian, T Tanaka, MK Wojczynski, A Hruby, L Djousse, JS Ngwa, JL Follis, M Dimitriou, A Ganna, DK Houston, S Kanoni, V Mikkilä, A Manichaikul, I Ntalla, F Renstrom, E Sonestedt, FJA van Rooij, S Bandinelli, L de Koning, U Ericson, N Hassanali, JC Kieft-de Jong, KK Lohman, O Raitakari, C Papoutsakis, P Sjogren, K Stirrups, E Ax, P Deloukas, CJ Groves, P Jacques, I Johansson, Y Liu, MI McCarthy, KE North, J Viikari, MC Zillikens, J Dupuis, A Hofman, G Kolovou, K Mukamal, I Prokopenko, O Rolandsson, I Seppälä, LA Cupples, FB Hu, M Kähönen, AG Uitterlinden, IB Borecki, L Ferrucci, DR Jacobs, Jr, SB Kritchevsky, M Orho-Melander, JS Pankow, T Lehtimäki, JCM Witteman, E Ingelsson, DS Siscovick, G Dedoussis, JB Meigs, PW Franks.

Gain-of-function Lipoprotein Lipase variant rs13702 modulates lipid traits through disruption of a microRNA-410 seed site. Am J Hum Genet, 92(1):5-14. PMID: 23246289 K Richardson, JA Nettleton; N Rotllan; T Tanaka; CE Smith; CQ Lai; LD Parnell; YC Lee; J Lahti; RN Lemaitre; A Manichaikul; M Keller; V Mikkila; J Ngwa; FJA Van Rooij; CM Ballentyne; IB Borecki; LA Cupples; M Garcia; A Hofman; L Ferrucci; D Mozaffarian; M Perälä; O Raitakari; Russell P Tracy; Donna K Arnett; Stefania Bandinelli; Eric Boerwinkle; JG Eriksson; OH Franco; M Kähönen; M Nalls; DS Siscovick; DK Houston; B Psaty; J Viikari; JCM Witteman; MO Goodarzi; T Lehtimaki; Y Liu; MC Zillikens; YDI Chen; AG Uitterlinden; JI Rotter; C Fernandez-Hernando; JM Ordovas.

Higher magnesium intake is associated with lower fasting glucose and insulin, with no evidence of interaction with select genetic loci, in a meta-analysis of 15 CHARGE consortium studies J Nutr, 143(3):345-53. PMID: 23343670 A Hruby, JS Ngwa, F Renström, MK Wojczynski, A Ganna, G Hallmans, DK Houston, PF Jacques, S Kanoni, T Lehtimäki, RN Lemaitre, A Manichaikul, KE North, I Ntalla, E Sonestedt, T Tanaka, FJA van Rooij, S Bandinelli, L Djoussé, E Grigoriou, I Johansson, KK. Lohman, JS. Pankow, OT Raitakari, U Risérus, M Yannakoulia, MC Zillikens, N Hassanali, Y Liu, D Mozaffarian, C Papoutsakis, AC Syvanen, AG. Uitterlinden, J Viikari, CJ Groves, A Hofman, L Lind, MI McCarthy, V Mikkilä, K Mukamal, OH Franco, IB Borecki, LA Cupples, GV Dedoussis, L Ferrucci, FB Hu, E Ingelsson, M Kähönen, WHL Kao, SB Kritchevsky, M Orho-Melander, I Prokopenko, JI Rotter, DS Siscovick, JCM Witteman, PW Franks, JB Meigs, NM McKeown, JA Nettleton

Lipoprotein receptor related protein 1 variants and dietary fatty acids for anthropometric traits: meta-analysis of 14 studies of European ancestry and 4 studies of African American ancestry Int J Obes

(Lond), 2013 Jan 29. PMID: 23357958; doi: 10.1038/ijo.2012.215 CE Smith, J Ngwa, T Tanaka, Q Qi, MK Wojczynski, R N Lemaitre, JS Anderson, A Manichaikul, V Mikkilä, FJA van Rooij, Z Ye, S Bandinelli, AC Frazier-Wood, DK Houston, F Hu, C Langenberg, NM McKeown, D Mozaffarian, KE North, J Viikari, MC Zillikens, L Djoussé, A Hofman, M Kähönen, EK Kabagambe, RJF Loos, GB Saylor, NG Forouhi, Y Liu, KJ Mukamal, YDI Chen, MY Tsai, AG Uitterlinden, O Raitakari, CM van Duijn, DK Arnett, IB Borecki, LA Cupples, L Ferrucci, SB Kritchevsky, T Lehtimäki, L Qi, JI Rotter, DS Siscovick, NJ Wareham, JCM Witteman, PhD; JM Ordovás, J A Nettleton.

Genome-wide meta-analysis of observational studies reveals common genetic variants associated with macronutrient intake Am J Clin Nutr. 2013 May 1 PMID: 23636237 T Tanaka, JS Ngwa, FJA van Rooij, MC Zillikens, MK Wojczynski, AC Frazier-Wood, DK Houston, S Kanoni, RN Lemaitre, J Luan, V Mikkilä, F Renstrom, E Sonestedt, JH Zhao, AY Chu, L Qi, DI Chasman, MC de Oliveira Otto, EJ Dhurandhar, MF Feitosa, I Johansson, K-T Khaw, K K Lohman, A Manichaikul, NM McKeown, D Mozaffarian, A Singleton, K Stirrups, J Viikari, Z Ye, S Bandinelli, I Barroso, P Deloukas, NG Forouhi, A Hofman, Y Liu, LP Lytykäinen, KE North, M Dimitriou, G Hallmans, M Kähönen, C Langenberg, JM Ordovas, AG Uitterlinden , FB Hu, IP Kalafati, O Raitakari, OH Franco, A Johnson, AS Plump, V Emilsson, JA Schrack, RD Semba, DS Siscovick, DK Arnett, IB Borecki, PW Franks, SB Kritchevsky, T Lehtimäki, RJF Loos, M Orho-Melander, JI Rotter, NJ Wareham, JCM Witteman, L Ferrucci, G Dedoussis, LA Cupples, JA Nettleton.

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Gene-environment interactions of circadian-related genes for cardiometabolic traits. Diabetes Care. (in press) Hassan S Dashti, Jack L Follis, Caren E Smith, Toshiko Tanaka, Marta Garaulet, Daniel J Gottlieb, Adela Hruby, Paul F Jacques, Jessica C Kieft-de Jong, Stefania Lamont-Fava, Frank AJL Scheer, Traci M Bartz, Leena Kovanen, Mary K Wojczynski, Alexis C Frazier-Wood, Tarunveer S Ahluwalia, Mia-Maria Perälä, Anna Jonsson, Taulant Muka, Ioanna P Kalafati, Vera Mikkilä, The CHARGE Nutrition Study Group, José M Ordovás.

Habitual sleep duration is associated with BMI and macronutrient intake, and may be modified by CLOCK genetic variants. American Journal of Clinical Nutrition . 101(1):135-43, 2015 Jan. Hassan S Dashti, Jack L Follis, Caren E Smith, Toshiko Tanaka, Brian E Cade, Daniel J Gottlieb, Adela Hruby, Paul F Jacques, Stefania Lamont-Fava, Kris Richardson, Richa Saxena, Frank AJL Scheer, Leena Kovanen, Traci M Bartz, Mia-Maria Perälä, Anna Jonsson, Alexis C Frazier-Wood, Ioanna-Panagiota Kalafati, Vera Mikkila,

Timo Partonen, Rozenn N Lemaitre, Jari Lahti, Dena G Hernandez, Ulla Toft, W Craig Johnson, Stavroula Kanoni, Olli T Raitakari, Markus Perola, Bruce M Psaty, Luigi Ferrucci, Niels Grarup, Heather M Highland, Loukianos Rallidis, Mika K Kähönen, Aki S Havulinna, David S Siscovick, Katri Raikkonen, Torben Jørgensen, Jerome I Rotter, Panos Deloukas, Jorma SA Viikari, Dariush Mozaffarian, Allan Linneberg, Ilkka Seppala, Torben Hansen, Veikko Salomaa, Sina A Gharib, Johan G Eriksson, Stefania Bandinelli, Oluf Pedersen, Stephen S Rich, George Dedoussis, Terho Lehtimäki, and Jose M Ordovas

FTO genetic variants, dietary intake, and body mass index: insights from 177,330 individuals. *Human Molecular Genetics*, 2014 Dec 20;23(25):6961-72. Q Qi, TO Kilpeläinen, MK Downe, TTanaka, CE Smith, I Sluijs, E Sonestedt, AY Chu, F Renström, X Lin, LH Ängquist, J Huang, Z Liu, Y Li, MA Ali, M Xu, TS Ahluwalia, JMA Boer, P Chen, M Daimon, J Eriksson, M Perola, Y Friedlander, Y-T Gao, DHM Heppe, JW Holloway, DK Houston, S Kanoni, Y-M Kim, MA Laaksonen, T Jääskeläinen, NR Lee, T Lehtimäki, RN Lemaitre, W Lu, RN Luben, A Manichaikul, S Männistö, P Marques-Vidal, K L Monda, JS Ngwa, L Perusse, FJA van Rooij, Y-B Xiang, W Wen, MK Wojczynski, J Zhu, IB Borecki, C Bouchard, Q Cai, C Cooper, GV Dedoussis, P Deloukas, L Ferrucci, NG Forouhi, T Hansen, L Christiansen, A Hofman, I Johansson, T Jørgensen, S Karasawa, KT Khaw, M-K Kim, K Kristiansson, H Li, X Lin, Y Liu, K K Lohman, J Long, V Mikkilä, D Mozaffarian, K North, O Pedersen, O Raitakari, H Rissanen, J Tuomilehto, YT van der Schouw, AG Uitterlinden, MC Zillikens, OH Franco, ES Tai, XO Shu, DS Siscovick, U Toft, WMM Verschuren, P Vollenweider, NJ Wareham, JCM Witteman, W Zheng, PM Ridker, JH. Kang, L Liang, MK Jensen.

Genome-wide meta-analysis identifies six novel loci associated with habitual coffee consumption. *Molecular Psychiatry*, 2015 May;20(5):647-56. The Coffee and Caffeine Genetics Consortium: MC Cornelis, EM Byrne, T Esko, MA Nalls, A Ganna, N Paynter, KL Monda, N Amin, K Fischer, F Renstrom, JS Ngwa, V Huikari, A Cavadino, IM Nolte, A Teumer, K Yu, P Marques-Vidal, R Rawal, A Manichaikul, MK Wojczynski, JM Vink, JH Zhao, G Burlutsky, J Lahti, V Mikkilä, RN Lemaitre, J Eriksson, SK Musani, T Tanaka, F Geller, J Luan, J Hui, R Mägi, M Dimitriou, ME Garcia, W-K Ho, MJ Wright, LM Rose, PKE Magnusson, NL Pedersen, D Couper, BA Oostra, A Hofman, MA Ikram, HW Tiemeier, AG Uitterlinden, FJA van Rooij, I Barroso, I Johansson, L Xue, M Kaakinen, L Milani, C Power, H Snieder, RP Stolk, SE Baumeister, R Biffar, F Gu, F Bastardot, Z Kutalik, DR Jacobs Jr, NG Forouhi, E Mihailov, L Lind, C Lindgren, K Michaëlsson, A Morris, M Jensen, K-T Khaw, RN Luben, JJ Wang, S Männistö, M-M Perälä, M Kähönen, T Lehtimäki, J Viikari, D Mozaffarian, K Mukamal, BM Psaty, A Döring, AC Heath, GW Montgomery, N Dahmen, T Carithers, KL Tucker, L Ferrucci, HA Boyd, M Melbye, JL Treur, D Mellström, JJ Hottenga, I Prokopenko, A Tönjes, P Deloukas, S Kanoni, M Lorentzon, DK Houston, Y Liu, J Danesh, A Rasheed, MA Mason, AB Zonderman, L Franke, BS Kristal, International Parkinson's Disease Genomics Consortium (IPDGC), North American Brain Expression Consortium (NABEC), UK Brain Expression Consortium (UKBEC), J Karjalainen, DR Reed, H-J Westra, MK Evans, D Saleheen, TB

Harris, G Dedoussis, G Curhan, M Stumvoll, J Beilby, LR Pasquale, B Feenstra, S Bandinelli, JM Ordovas, AT Chan, U Peters, C Ohlsson, C Gieger, NG Martin, M Waldenberger, DS Siscovick, O Raitakari, JG Eriksson, P Mitchell, DJ Hunter, P Kraft, EB Rimm, DI Boomsma, IB Borecki, RJF Loos, NJ Wareham, P Vollenweider, N Caporaso, HJ Grabe, ML Neuhausen, BHR Wolffensuttel, FB Hu, , E Hyppönen, M-R Järvelin, LA Cupples, PW Franks, PM Ridker, CM van Duijn, G Heiss, A Metspalu, KE North, E Ingelsson, JA Nettleton, RM van Dam, DI Chasman

Genexdietary pattern interactions in obesity: analysis of up to 68,317 adults of European ancestry Hum. Mol. Genet. first published online May 20, 2015 doi:10.1093/hmg/ddv186

Nettleton JA, Follis JL, Ngwa JS, Smith CE, Ahmad S, Tanaka T, Wojczynski MK, Voortman T, Lemaitre RN, Kristiansson K, Nuotio ML, Houston DK, Perälä MM, Qi Q, Sonestedt E, Manichaikul A, Kanoni S, Ganna A, Mikkilä V, North KE, Siscovick DS, Harald K, McKeown NM, Johansson I, Rissanen H, Liu Y, Lahti J, Hu FB, Bandinelli S, Rukh G, Rich S, Booij L, Dmitriou M, Ax E, Raitakari O, Mukamal K, Männistö S, Hallmans G, Jula A, Ericson U, Jacobs DR Jr, van Rooij FJ, Deloukas P, Sjögren P, Kähönen M, Djousse L, Perola M, Barroso I, Hofman A, Stirrups K, Viikari J, Uitterlinden AG, Kalafati IP, Franco OH, Mozaffarian D, Salomaa V, Borecki IB, Knekt P, Kritchevsky SB, Eriksson JG, Dedoussis GV, Qi L, Ferrucci L, Orho-Melander M, Zillikens MC, Ingelsson E, Lehtimäki T, Renström F, Cupples LA, Loos R, Franks PW.

E. Grants:

Genetic predictors of dairy intake and metabolic responses to dairy foods Funding agency: NIH NHLBI
K08 PI: Caren Smith Submitted: 2012 Current Status: awarded

Genetic determinants of taste preferences and risk of metabolic disease Funding agency: NIH National Institute on Deafness and other Communication Disorders NIDCD R03 PI: Marilyn Cornelis Submitted: October 31, 2012 Current Status: awarded

Interactions between Sugar-Sweetened Beverage Consumption and ChREBP in the Development of Insulin Resistance Funding agency: Boston Area Diabetes Endocrinology Research Center (BADERC)
PI: Nicola McKeown Current Status: Funded 2015

A Multi-Ethnic Study of Gene-Lifestyle Interactions in Cardiovascular Traits Funding agency: NIH/NHLBI
R01 PI: DC Rao, Ingrid Borecki Current Status: Funded, project to be carried out in new Lifestyle Interaction Working Group *NutrWG will contribute diet score

Pharmacogenetics

- A. Phenotypes: Drug gene-interactions across a variety of phenotypes
- B. Phenotypes actively being analyzed: Electrocardiographic QT interval, RR interval; low-density lipoprotein cholesterol; high-density lipoprotein cholesterol; triglycerides; glucose and insulin; potassium; heart rate; blood pressure and hypertension; and cardiovascular events.
- C. WG Leaders: Bruce Psaty psaty@u.washington.edu
- D. Publications:

Postmus I, Trompet S, Deshmukh HA, Barnes MR, Li X, Warren HR, Chasman DI, Zhou K, Arsenault BJ, Donnelly LA, Wiggins KL, Avery CL, Griffin P, Feng Q, Taylor KD, Li G, Evans DS, Smith AV, de Keyser CE, Johnson AD, de Craen AJ, Stott DJ, Buckley BM, Ford I, Westendorp RG, Slagboom PE, Sattar N, Munroe PB, Sever P, Poulter N, Stanton A, Shields DC, O'Brien E, Shaw-Hawkins S, Chen YD, Nickerson DA, Smith JD, Dubé MP, Boekholdt SM, Hovingh GK, Kastelein JJ, McKeigue PM, Betteridge J, Neil A, Durrington PN, Doney A, Carr F, Morris A, McCarthy MI, Groop L, Ahlqvist E; Wellcome Trust Case Control Consortium, Bis JC, Rice K, Smith NL, Lumley T, Whitsel EA, Stürmer T, Boerwinkle E, Ngwa JS, O'Donnell CJ, Vasan RS, Wei WQ, Wilke RA, Liu CT, Sun F, Guo X, Heckbert SR, Post W, Sotoodehnia N, Arnold AM, Stafford JM, Ding J, Herrington DM, Kritchevsky SB, Eiriksdottir G, Launer LJ, Harris TB, Chu AY, Giulianini F, MacFadyen JG, Barratt BJ, Nyberg F, Stricker BH, Uitterlinden AG, Hofman A, Rivadeneira F, Emilsson V, Franco OH, Ridker PM, Gudnason V, Liu Y, Denny JC, Ballantyne CM, Rotter JI, Adrienne Cupples L, Psaty BM, Palmer CN, Tardif JC, Colhoun HM, Hitman G, Krauss RM, Wouter Jukema J, Caulfield MJ. Pharmacogenetic meta-analysis of genome-wide association studies of LDL cholesterol response to statins. *Nat Commun.* 2014 Oct 28;5:5068. doi: 10.1038/ncomms6068. PubMed PMID: 25350695; PubMed Central PMCID: PMC4220464.

Sitlani CM, Rice KM, Lumley T, McKnight B, Cupples LA, Avery CL, Noordam R, Stricker BH, Whitsel EA, Psaty BM. Generalized estimating equations for genome-wide association studies using longitudinal phenotype data. *Stat Med.* 2015 Jan 15;34(1):118-30. doi: 10.1002/sim.6323. Epub 2014 Oct 9. PubMed PMID: 25297442; PubMed Central PMCID: PMC4321952.

Avery CL, Der JS, Whitsel EA, Stürmer T. Comparison of study designs used to detect and characterize pharmacogenomic interactions in nonexperimental studies: a simulation study. *Pharmacogenet Genomics.* 2014 Mar;24(3):146-55. doi:10.1097/FPC.0000000000000027. PubMed PMID: 24413365; PubMed Central PMCID: PMC3946643.

Avery CL, Sitlani CM, Arking DE, Arnett DK, Bis JC, Boerwinkle E, Buckley BM, Ida Chen YD, de Craen AJ, Eijgelsheim M, Enquobahrie D, Evans DS, Ford I, Garcia ME, Gudnason V, Harris TB, Heckbert SR,

Hochner H, Hofman A, Hsueh WC, Isaacs A, Jukema JW, Knekt P, Kors JA, Krijthe BP, Kristiansson K, Laaksonen M, Liu Y, Li X, Macfarlane PW, Newton-Cheh C, Nieminen MS, Oostra BA, Peloso GM, Porthan K, Rice K, Rivadeneira FF, Rotter JI, Salomaa V, Sattar N, Siscovick DS, Slagboom PE, Smith AV, Sotoodehnia N, Stott DJ, Stricker BH, Stürmer T, Trompet S, Uitterlinden AG, van Duijn C, Westendorp RG, Witteman JC, Whitsel EA, Psaty BM. Drug-gene interactions and the search for missing heritability: a cross-sectional pharmacogenomics study of the QT interval. *Pharmacogenomics J.* 2014 Feb;14(1):6-13. doi: 10.1038/tpj.2013.4. Epub 2013 Mar 5. PubMed PMID: 23459443; PubMed Central PMCID: PMC3766418.

E. Grants:

R01 HL103612 supports the pharmacogenetics working group.

Recently funded, an American Heart Association Grant, PI, Christy Avery.

Physical Activity

- A. Phenotypes: Submaximum exercise heart rate at 50 Watts and 100 Watts, Submaximum exercise systolic blood pressure at 50 Watts and 100 Watts, Submaximum exercise diastolic blood pressure at 50 Watts and 100 Watts, Maximum exercise cap (peak VO₂ (ml/kg/min), measured/ estimated from workload achieved)
- B. Phenotypes actively being analyzed:
- C. WG Leaders: Greg Lewis GLEWIS@PARTNERS.ORG, Thomas Wang TJWANG@mgh.harvard.edu
- D. Publications: none
- E. Grants: none

Pulmonary

- A. Phenotypes: Continuous parameters of pulmonary function (FEV1, FEV1/FVC, FVC) both cross-sectional and longitudinal, Airflow obstruction, Asthma, Pneumonia
- B. Phenotypes actively being analyzed: FEV1, FVC, FEV1/FVC, airflow obstruction
- C. WG Leaders: Stephanie London london2@niehs.nih.gov
- D. Publications:

Meta-analyses of genome-wide association studies identify multiple loci associated with pulmonary function. Nat Genet 2010 Jan; 42(1):45-52

Genome-wide association and large-scale follow up identifies 16 new loci influencing lung function. Nat Genet 2011; 43:1082-1090

Genome-Wide Association Studies Identify CHRNA5/3 and HTR4 in the Development of Airflow Obstruction. Am. J. Respir. Crit. Care Med. October 1, 2012 vol. 186 no. 7 622-632

Genome-wide joint meta-analysis of SNP and SNP-by-smoking interaction identifies novel loci for pulmonary function - FEV1 and FEV1/FVC – PLOS Genetics 2012;8(12):e1003098. Epub 2012 Dec 20

London SJ, Gao W, Gharib SA, Hancock DB, Wilk JB, Gibbs RA, Muzny DM, Lumley T, House JS, Franceschini N, North KE, Psaty BM, Kovar CL, Coresh J, Zhou Y, Heckbert SR, Brody JA, Morrison AC, Dupuis J. ADAM19 and HTR4 variants in relation to pulmonary function: the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Targeted Sequencing Study. Circulation Cardiovascular Genetics. Circ Cardiovasc Genet. 2014 Jun;7(3):350-8. doi: 10.1161/CIRCGENETICS.113.000066. PMID: 24951661

Loth DW, Artigas MS, Gharib SA, Wain LV, Franceschini N, Koch B, Pottinger TD, Smith AV, Duan Q, Oldmeadow C, Lee MK, Strachan DP, James AL, Huffman JE, Vitart V, Ramasamy A, Wareham NJ, Kaprio J, Wang XQ, Trochet H, Kähönen M, Flexeder C, Albrecht E, Lopez LM, de Jong K, Thyagarajan B, Alves AC, Enroth S, Omenaa E, Joshi PK, Fall T, Viñuela A, Launer LJ, Loehr LR, Fornage M, Li G, Wilk JB, Tang W, Manichaikul A, Lahousse L, Harris TB, North KE, Rudnicka AR, Hui J, Gu X, Lumley T, Wright AF, Hastie ND, Campbell S, Kumar R, Pin I, Scott RA, Pietiläinen KH, Surakka I, Liu Y, Holliday EG, Schulz H, Heinrich J, Davies G, Vonk JM, Wojczynski M, Pouta A, Johansson A, Wild SH, Ingelsson E, Rivadeneira F, Völzke H, Hysi PG, Eiriksdottir G, Morrison AC, Rotter JI, Gao W, Postma DS, White WB, Rich SS, Hofman A, Aspelund T, Couper D, Smith LJ, Psaty BM, Lohman K, Burchard EG, Uitterlinden AG, Garcia M, Joubert BR, McArdle WL, Musk AB, Hansel N, Heckbert SR, Zgaga L, van

Meurs JB, Navarro P, Rudan I, Oh YM, Redline S, Jarvis DL, Zhao JH, Rantanen T, O'Connor GT, Ripatti S, Scott RJ, Karrasch S, Grallert H, Gaddis NC, Starr JM, Wijmenga C, Minster RL, Lederer DJ, Pekkanen J, Gyllensten U, Campbell H, Morris AP, Gläser S, Hammond CJ, Burkart KM, Beilby J, Kritchevsky SB, Gudnason V, Hancock DB, Williams OD, Polasek O, Zemunik T, Kolcic I, Petrini MF, Wijst M, Kim WJ, Porteous DJ, Scotland G, Smith BH, Viljanen A, Heliövaara M, Attia JR, Sayers I, Hampel R, Gieger C, Deary IJ, Boezen HM, Newman A, Jarvelin MR, Wilson JF, Lind L, Stricker BH, Teumer A, Spector TD, Melén E, Peters MJ, Lange LA, Barr RG, Bracke KR, Verhamme FM, Sung J, Hiemstra PS, Cassano PA, Sood A, Hayward C, Dupuis J, Hall IP, Brusselle GG, Tobin MD, London SJ. Genome-wide association analysis identifies six new loci associated with forced vital capacity. *Nat Genet.* 2014 Jul;46(7):669-77. doi: 10.1038/ng.3011. Epub 2014 Jun 15. PMID: 24929828,

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E. Grants:

Promising scores received on two grants submitted from the group in response to a gene-environment RFA.

Renal

A. Phenotypes: glomerular filtration rate (GFR) based on serum creatinine and serum cystatin C, urinary albumin-to-creatinine ratio, chronic kidney disease (CKD), serum electrolyte concentrations (calcium, phosphate, sodium, potassium, magnesium), kidney stones, serum uric acid levels, gout.

B. Phenotypes actively being analyzed:

C. WG Leaders: Caroline Fox foxca@nhlbi.nih.gov, Ann Kottgen akottgen@jhsph.edu

D. Publications:

Association of three genetic loci with uric acid concentration and risk of gout: a genome-wide association study. *Lancet*. 2008 Dec 6;372(9654):1953-61. PMID: 18834626

Multiple loci associated with indices of renal function and chronic kidney disease. *Nat Genet* 2009;41(6):712-717. PMID: 19430482

New loci associated with kidney function and chronic kidney disease. *Nat Genet*. 2010 May;42(5):376-84. PMID: 20383146

Association of eGFR-related loci identified by GWAS with incident CKD and ESRD. *PLoS Genet*. 2011 Sep;7(9):e1002292. Epub 2011 Sep 29. PubMed PMID: 21980298; PubMed Central PMCID: PMC3183079.

Genetic Association for Renal Traits among Participants of African Ancestry Reveals New Loci for Renal Function. *PLoS Genet*. 2011 Sep;7(9):e1002264. Epub 2011 Sep 8. PubMed PMID: 21931561; PubMed Central PMCID: PMC3169523.

Genome-wide association study for serum urate concentrations and gout among African Americans identifies genomic risk loci and a novel URAT1 loss-of-function allele. *Hum Mol Genet*. 2011 Oct 15;20(20):4056-4068. Epub 2011 Jul 18. PubMed PMID: 21768215; PubMed Central PMCID: PMC3177647

CUBN is a gene locus for albuminuria. *J Am Soc Nephrol*. 2011 Mar;22(3):555-70. PubMed PMID: 21355061; PubMed Central PMCID: PMC3060449.

Multiple genetic loci influence serum urate levels and their relationship with gout and cardiovascular disease risk factors. *Circ Cardiovasc Genet*. 2010 Dec;3(6):523-30. Epub 2010 Sep 30. PubMed PMID: 20884846.

A common variants in the calcium-sensing receptor gene are associated with total serum calcium levels. Hum Mol Genet. 2010 Nov 1;19(21):4296-303. Epub 2010 Aug 12. PubMed PMID: 20705733; PubMed Central PMCID: PMC2951868.

Genetic Factors for Osteoporosis Consortium; Meta Analysis of Glucose and Insulin Related Traits Consortium. Genome-wide association studies of serum magnesium, potassium, and sodium concentrations identify six Loci influencing serum magnesium levels. PLoS Genet. 2010 Aug 5;6(8). pii: e1001045. PubMed PMID: 20700443; PubMed Central PMCID: PMC2916845.

Common genetic variants associate with serum phosphorus concentration. J Am Soc Nephrol. 2010 Jul;21(7):1223-32. Epub 2010 Jun 17. PubMed PMID: 20558539; PubMed Central PMCID: PMC3152230.

Genetic association for renal traits among participants of African ancestry reveals new loci for renal function. PLoS Genet. 2011 Sep;7(9):e1002264. Epub 2011 Sep 8. PMID: 21931561.

Association of eGFR-Related Loci Identified by GWAS with Incident CKD and ESRD. PLoS Genet. 2011 Sep;7(9):e1002292. Epub 2011 Sep 29. PMID: 21980298. Genome-wide Association and Functional Follow-Up Reveals New Loci for Kidney Function. PLoS Genet. 2012 Mar;8(3):e1002584. Epub 2012 Mar 29. PMID: 22479191.

Genome-wide Association and Functional Follow-Up Reveals New Loci for Kidney Function. PLoS Genet. 2012 Mar;8(3):e1002584. Epub 2012 Mar 29. PMID: 22479191.

Association of estimated glomerular filtration rate and urinary uromodulin concentrations with rare variants identified by UMOD gene region sequencing. PLoS One. 2012;7(5):e38311. Epub 2012 May 31. PMID: 22693617.

Meta-analysis identifies multiple loci associated with kidney function-related traits in east Asian populations. Nat Genet. 2012 Jul 15;44(8):904-9. PMID: 22797727.

Integration of genome-wide association studies with biological knowledge identifies six novel genes related to kidney function. Hum Mol Genet. 2012 Sep 25. [Epub ahead of print] PMID: 22962313

Genome-wide association analyses identify 18 new loci associated with serum urate concentrations. Nat Genet. 2013 Feb;45(2):145-54. doi: 10.1038/ng.2500. Epub 2012 Dec 23. PMID: 23263486

Overlap Between Common Genetic Polymorphisms Underpinning Kidney Traits Cardiovascular Disease Phenotypes: The CKDGen Consortium. Am J Kidney Dis. 2013 Mar 6. doi:pii: S0272-6386(13)00029-2. 10.1053/j.ajkd.2012.12.024. [Epub ahead of print] PMID: 23474010

E. Grants:

Next-Generation Medical Resequencing of Gout Disease Genes in the ARIC Cohort Principal Investigator: James Hixson PhD, University of Texas Health Sciences Agency: NHGRI Type: 5RC2HG005697-02, Period 2010-2012

Exome sequence analysis of CKD Principal Investigator: W. H. Linda Kao PhD, Johns Hopkins University Agency: NIDDK Type: 3R01DK076770-04S1

Repro-GEN

A. Phenotypes: Age at menarche, Age at natural menopause

B. Phenotypes actively being analyzed:

C. WG Leaders: Joanne Murabito murabito@bu.edu, Andre Uitterlinden a.g.uitterlinden@erasmusmc.nl

D. Publications:

Perry JR, Stolk L, Franceschini N, Lunetta KL, Zhai G, McArdle PF et al. Meta-analysis of genome-wide association data identifies two loci influencing age at menarche. *Nat Genet* 2009; 41(6):648-650.

Sulem P, Gudbjartsson DF, Rafnar T, Holm H, Olafsdottir EJ, Oladsdottir GH et al. Genome-wide association study identifies sequence variants on 6q21 associated with age at menarche. *Nat Genet*, 2009

He C, Kraft P, Chen C, Buring JE, Pare G, Hankinson SE et al. Genome-wide association studies identify loci associated with age at menarche and age at natural menopause. *Nat Genet* 2009.

Stolk L, Zhai G, van Meurs JB, Verbiest MM, Visser JA, Estrada K et al. Loci at chromosomes 13, 19 and 20 influence age at natural menopause. *Nat Genet* 2009.

Elks CE, Perry JR, Sulem P, Chasman DI, Franceschini N, He C et al. Thirty new loci for age at menarche identified by a meta-analysis of genome-wide association studies. *Nat Genet* 2010; 42(12):1077-1085

Stolk L, Perry JR, Chasman DI, He C, Mangino M, Sulem P et al. Meta-analyses identify 13 loci associated with age at menopause and highlight DNA repair and immune pathways. *Nat Genet* 2012

He C, Chasman DI, Dreyfus J, Hwang SJ, Ruiter R, Sanna S et al. Reproductive aging associated common genetic variants and the risk of breast cancer. *Breast Cancer Res* 2012; 14(2):R54.

Perry JR, Corre T, Esko T, Chasman DI, Fischer K, Franceschini N, He C, Kutalik Z, Mangino M, Rose LM, Vernon Smith A, Stolk L, Sulem P, Weedon MN, Zhuang WV, Arnold A, Ashworth A, Bergmann S, Buring JE, Burri A, Chen C, Cornelis MC, Couper DJ, Goodarzi MO, Gudnason V, Harris T, Hofman A, Jones M, Kraft P, Launer L, Laven JS, Li G, McKnight B, Masciullo C, Milani L, Orr N, Psaty BM, Ridker PM, Rivadeneira F, Sala C, Salumets A, Schoemaker M, Traglia M, Waeber G, Chanock SJ, Demerath EW, Garcia M, Hankinson SE, Hu FB, Hunter DJ, Lunetta KL, Metspalu A, Montgomery GW, Murabito JM, Newman AB, Ong KK, Spector TD, Stefansson K, Swerdlow AJ, Thorsteinsdottir U, Van Dam RM, Uitterlinden AG, Visser JA, Vollenweider P, Toniolo D, Murray A. A genome-wide association study of early menopause and the combined impact of identified variants. *Hum Mol Genet*. 2013 Jan 21.

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Perry JR, Hsu YH, Chasman DI, et al. DNA mismatch repair gene MSH6 implicated in determining age at natural menopause. *Human molecular genetics* 2013.

Perry JR, Day F, Elks CE, Sulem P,, Murray A, Easton DF, Stefansson K, Murabito JM, Ong KK. Parent-of-origin-specific allelic associations among 106 genomic loci for age at menarche. *Nature*. 2014 Jul 23.

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Chen CT, Liu CT, Chen GK, Andrews JS, Arnold AM, Dreyfus J, Franceschini N, Garcia ME, Kerr KF, Li G, Lohman KK, Musani SK, Nalls MA, Raffel LJ, Smith J, Ambrosone CB, Bandera EV, Bernstein L, Britton A, Brzyski RG, Cappola A, Carlson CS, Couper D, Deming SL, Goodarzi MO, Heiss G, John EM, Lu X, Le Marchand L, Marciante K, McKnight B, Millikan R, Nock NL, Olshan AF, Press MF, Vaiyda D, Woods NF, Taylor HA, Zhao W, Zheng W, Evans MK, Harris TB, Henderson BE, Kardia SL, Kooperberg C, Liu Y, Mosley TH, Psaty B, Wellons M, Windham BG, Zonderman AB, Cupples LA, Demerath EW, Haiman C, Murabito JM, Rajkovic A. Meta-analysis of loci associated with age at natural menopause in african-american women. *Human molecular genetics*. 2014;23:3327-3342

Lunetta KL, Day F, Sulem P, Ruth KS, Tung JY, Hinds DA, et al. Rare coding variants and X-linked loci associated with age at menarche. *Nat Commun* in press

Day FR, Ruth KS, Thompson DJ, Lunetta KL, Pervjakova N, Chasman DI, et al. Large-scale genomic analyses link reproductive ageing to hypothalamic signaling, breast cancer susceptibility and BRCA1-mediated DNA double strand break repair under review

Locke AE, Kahali B, Berndt SI, et al. Genetic studies of body mass index yield new insights for obesity biology. *Nature*. Feb 12 2015;518(7538):197-206.

Shungin D, Winkler TW, Croteau-Chonka DC, et al. New genetic loci link adipose and insulin biology to body fat distribution. *Nature*. Feb 12 2015;518(7538):187-196.

E. Grants: no information

Sex Hormone

A. Phenotypes: Sex hormones: Total Testosterone, Free Testosterone, SHBG, DHEAS, Estradiol, Estrone

B. Phenotypes actively being analyzed:

C. WG Leaders: Joanne Murabito murabito@bu.edu, Claes Ohlsson claes.ohlsson@medic.gu.se

D. Publications:

Coviello AD, Haring R, Wellons M, Vaidya D, Lehtimaki T, Keildson S, et al, A Genome-Wide Association Study Meta-Analysis of Circulating Sex Hormone Binding Globulin Reveals Multiple Loci Implicated in Sex Steroid Hormone Regulation. PLoS Genet 2012; 8 (7): e1002805.

Zhai G, Teumer A, Stolk L, Perry JR, Vandenput L, Coviello AD et al. Eight common genetic variants associated with serum DHEAS levels suggest a key role in ageing mechanisms. PLoS Genet 2011; 7(4):e1002025.

Ohlsson C, Wallaschofski H, Lunetta KL, Stolk L, Perry JR, Koster A et al. Genetic determinants of serum testosterone concentrations in men. PLoS Genet 2011; 7(10):e1002313.

E. Grants: none

Sleep

- A. Phenotypes: Sleep
- B. Phenotypes actively being analyzed:
- C. WG Leaders: Daniel Gottlieb DJGOTTLIEB@PARTNERS.ORG, Henning Tiemeier h.tiemeier@erasmusmc.nl, John Robbins jarobbins@ucdavis.edu
- D. Publications: none
- E. Grants: none

Subclinical / CHD

- A. Phenotypes: Coronary Heart Disease, Myocardial Infarction: prevalent, incident, and post-event mortality, Carotid Artery traits by ultrasound: common carotid intima media thickness (IMT); internal carotid IMT, presence of plaque or stenosis, Coronary Artery Calcium (CAC) traits by computed tomography: level & presence of CAC, Peripheral artery disease traits: Ankle-Brachial Index (ABI), presence of PAD
- B. Phenotypes actively being analyzed:
- C. WG Leaders: Josh Bis joshbis@u.washington.edu, Joanne Murabito murabito@bu.edu, Christopher O'Donnell odonnellc@nhlbi.nih.gov
- D. Publications:

Sequencing of 2 Subclinical Atherosclerosis Candidate Regions in 3669 Individuals: Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium Targeted Sequencing Study. Circ Cardiovasc Genet. (2014) doi: 10.1161/CIRCGENETICS.113.000116

Association Between Chromosome 9p21 Variants and the Ankle-Brachial Index Identified by a Meta-Analysis of 21 Genome-Wide Association Studies. Circ Cardiovasc Genet. (2012)
doi:10.1161/CIRCGENETICS.111.961292

Genome-Wide Association Study for Coronary Artery Calcification With Follow-Up in Myocardial Infarction. Circulation (2011) doi: 10.1161/CIRCULATIONAHA.110.974899

Meta-analysis of genome-wide association studies from the CHARGE consortium identifies common variants associated with carotid intima media thickness and plaque. Nature Genetics (2011)
doi:10.1038/ng.920

- E. Grants: none

Sudden Cardiac Arrest

- A. Phenotypes: Sudden cardiac arrest
- B. Phenotypes actively being analyzed:
- C. WG Leaders: David Siscovick dsiscovick@nyam.org, Nona Sotoodehnia nsotoo@u.washington.edu
- D. Publications:

Arking et al, "Identification of a sudden cardiac death susceptibility locus through GWAS in European ancestry individuals." PloS Genetics 2011

- E. Grants:

Genomics of Sudden Cardiac Arrest among African Americans, NIH R01, 2012-2016

Telomeres

- A. Phenotypes: Leukocyte telomere length
- B. Phenotypes actively being analyzed:
- C. WG Leaders: Dan Levy levyd@nhlbi.nih.gov
- D. Publications:

Genome-wide association identifies OBFC1 as a locus involved in human leukocyte telomere biology.

Proceedings of the National Academy of Sciences 2010;107(20):9293-9298.

- E. Grants:

R01AG20132, A. Aviv, PI

R01AG021593, A. Aviv , PI

R01AG030678, A. Aviv, PI

R01HL080698, A. Fitzpatrick, PI

R01AG16592, G. Berenson, PI

Thyroid Function

- A. Phenotypes: TSH, FT4, TPO antibodies, subclinical and overt hypo- and hyperthyroidism
- B. Phenotypes actively being analyzed: Subclinical and overt hypo- and hyperthyroidism, TSH and FT4
- C. WG Leaders: Robin Peeters robin.peeters@gmail.com, Marco Medici m.medici@erasmusmc.nl,
Anna Cappola acappola@mail.med.upenn.edu
- D. Publications:

Porcu E, Medici M, and Pistis G et al. A meta-analysis of thyroid-related traits reveals novel loci and gender-specific differences in the regulation of thyroid function. PLoS Genet, 2013, 9(2):e1003266.

Medici M, Porcu E, and Pistis G et al. Identification of Novel Genetic Loci Associated with Thyroid Peroxidase Antibodies and Clinical Thyroid Disease. PLoS Genet, 2014, 10(2):e1004123.

Kuś A, Szymański K, Peeters RP, Miśkiewicz P, Porcu E, Pistis G, Sanna S, Naitza S, Płoski R, Medici M, Bednarczuk T. The association of thyroid peroxidase antibody risk loci with susceptibility to and phenotype of Graves' disease. Accepted in Clin Endocrinol.

Schultheiss UT, Teumer A, Medici M, Li Y, Daya N, Chaker L, Hornuth G, Uitterlinden AG, Nauck M, Hofman A, Selvin E, Völzke H, Peeters RP, Köttgen A. A genetic risk score for thyroid peroxidase antibodies associates with clinical thyroid disease in community-based populations. J Clin Endocrinol Metab. 2015, 100(5):E799-807.

- E. Grants: none

Tonometry

- A. Phenotypes: PWV
- B. Phenotypes actively being analyzed:
- C. WG Leaders: Gary Mitchell GaryFMitchell@Mindspring.com, Dan Levy levyd@nhlbi.nih.gov
- D. Publications:
Mitchell, et al., Common genetic variation in the 3'-BCL11B gene desert is associated with carotid-femoral pulse wave velocity and excess cardiovascular disease risk: the AortaGen Consortium. *Circ Cardiovasc Genet.* 2012;5:81-90.

Wain, et al., Genome-wide association study identifies six new loci influencing pulse pressure and mean arterial pressure. *Nat Genet.* 2011;43:1005-11.

Durik, et al., Nucleotide excision DNA repair is associated with age-related vascular dysfunction. *Circulation.* 2012;126:468-478.

Olden, et al., Overlap between Common Genetic Polymorphisms Underpinning Kidney Traits and Cardiovascular Disease Phenotypes: The CKDGen Consortium. *Am J Kidney Dis.* 2013;61:889-898.

Beygui, et al., Adrenomedullin and arterial stiffness: integrative approach combining monocyte ADM expression, plasma MR-Pro-ADM, and genome-wide association study. *Circ Cardiovasc Genet.* 2014;7:634-641.

The Interleukin 1 Genetics Consortium. Cardiometabolic effects of genetic upregulation of the interleukin 1 receptor antagonist: a Mendelian randomisation analysis. *Lancet Diabetes Endocrinol.* 2015;3:243-253.

- E. Grants: none

Venous Thromboembolism

A. Phenotypes: Venous thrombosis and pulmonary embolism

B. Phenotypes actively being analyzed: VTE

C. WG Leaders: Weihong Tang tang0097@umn.edu

D. Publications:

Tang W, Teichert M, Chasman D, Heit J, Morange P, Li G, Pankratz N, Leebeek F, Pare G, de Andrade M, Tsourio C, Psaty B, Basu S, Ruiter R, Rose L, Armasu S, Lumley T, Heckbert S, Uitterlinden A, Lathrop M, Rice K, Cushman M, Hofman A, Lambert J-C, Glazer N, Pankow J, Witteman J, Amouyel P, Bis J, Bovill E, Kong X, Tracy R, Boerwinkle E, Rotter J, Tre'goue't D-A, Loth D, Stricker B, Ridker P, Folsom A, Smith N. A genome-wide association study for venous thromboembolism: the extended Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium. *Genet Epidemiol* 2013;37(5):512-521. PMCID: PMID: 23650146

Germain M, Chasman DI, de Haan H, Tang W, Lindstrom S, Weing LC, de Andrade M, de Visser MCH, Wiggins KL, Suchon P, Saut N, Smadja DM, Le Gal G, van Hylckama Vlieg A, Di Narzo A, Hao K, Nelson CP, Rocamin-Arjo A, Folkersen L, Monajemi R, Rose LM, Brody JA, Slagboom E, Aissi D, Gagnon F, Deleuze JF, Deloukas P, Tzourio C, Dartigues JF, Berr C, Taylor KD, Civelek M, Eriksson P, Cardiogenics Consortium, Psaty BM, Houwing-Duitermaat J, Goodall AH, Cambien F, Kraft P, Amouyel P, Samani NJ, Basu S, Ridker PM, Rosendaal FR, Kabrhel C, Folsom AR, Heit J, Reitsma PH, Tregouet DA, Smith NL, Morange PE, on behalf of the INVENT consortium. Meta-analysis of 65,734 individuals identifies TSPAN15 and SLC44A2 as two susceptibility loci for venous thromboembolism. *American Journal of Human Genetics* 2015 Mar 11. pii: S0002-9297(15)00051-8. doi: 10.1016/j.ajhg.2015.01.019. [Epub ahead of print]

E. Grants:

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