BIOGRAPHICAL SKETCH

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NAME: Klarin, Derek

eRA COMMONS USER NAME (credential, e.g., agency login): DEREKKLARIN

POSITION TITLE: Assistant Professor of Surgery, Stanford University Medical Center/VA Palo Alto Health Care System in Palo Alto, CA

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Cornell University	B.A.	06/2007	Biological Sciences, Chemical Sciences - Double Major
University of California, Los Angeles, School of Medicine	M.D.	06/2012	Medicine
Broad Institute of Harvard and MIT	Fellow	06/2017	Research Fellowship - Statistical Genetics
Massachusetts General Hospital	Resident	06/2019	General Surgery
University of Florida College of Medicine, Shands Hospital	Fellow	07/2021	Vascular Surgery

A. Personal Statement

My research uses genomic approaches to better understand the etiology of atherosclerosis, vascular disease, and their associated risk factors including lipids and thrombosis. I have formal training in general and vascular surgery from the Massachusetts General Hospital and the University of Florida respectively, with a strong background in statistical genetics through extensive post-doctoral work at the Broad Institute of Harvard and MIT. As a vascular surgeon, I have focused specifically on understanding the driving factors that cause vascular disease in one vascular bed (coronary, cerebral, peripheral, or venous) over another, as well as the underlying genetic factors that contribute to abdominal aortic aneurysm (AAA). To achieve this, I have focused on (1) variant/gene discovery; (2) phenotyping strategies utilizing large-scale electronic health record (EHR) data to increase discovery power; (3) defining the mechanisms by which newly identified mutations (germline and somatic) impact disease; (4) leveraging these insights for preventative and therapeutic intervention. I have extensive experience in bioinformatics using two large-scale EHR based health systems (UK National Health Service, VA Healthcare System) to identify those with vascular disease for genetic analysis.

I also investigate individuals at risk for atherosclerosis due to clonal hematologic malignancy precursors, such as clonal hematopoiesis of indeterminate potential (CHIP). This research focuses on acquired somatic mutations in hematopoietic cells predisposing to clonal hematopoiesis associated with risk for atherosclerotic cardiovascular disease, with a specific focus on peripheral artery disease (PAD).

In collaboration with other VA investigators, I lead a research effort to elucidate the genetic basis of complex vascular disease traits in the VA Million Veteran Program (MVP). Our recent work has expanded our understanding of genetics of lipids as well as arterial and venous disease through large-scale genetic analysis in over 750,000 Veterans. By combining methods in computational biology, statistics, and epidemiology, I use the discovered risk genes/mutations to identify those at greatest risk for lower extremity ischemia, thrombosis, and limb amputation. Two of my manuscripts in this space were recognized as among the top advances in heart disease and stroke research in 2019 by the American Heart Association.

B. Positions and Honors

Academic and Clinical Appointments

2012-2019 Clinical Resident in General Surgery, Massachusetts General Hospital/Harvard Medical School, Boston, MA

2019- Clinical Fellow in Vascular Surgery, University of Florida College of Medicine/Shands Hospital, Gainesville, FL

2015- Affiliated Scientist, Broad Institute of Harvard and MIT, Cambridge, MA

Other Experience and Professional Memberships

2012-2019 Member, Massachusetts Medical Society

2016- Member, American Heart Association, Council on Peripheral Vascular Disease

2017- Member, Global Lipids Genetics Consortium

2018- Ad hoc reviewer - *Eur Heart J, Arterioscl Thromb Vasc Biol, Ann Surg, Circ Genom Precis Med, PLOS Genetics, PLOS One, JACC, Cell Reports Medicine, JAMA Cardiol*

2019- Member, Society for Vascular Surgery

2019- Founding Member, Abdominal Aortic Aneurysm Genetics Consortium (AAAGen)

2020- Founding Member, Peripheral Artery Disease Genetics Consortium (PADGen)

Honors

2006 Howard Hughes Undergraduate Research Fellowship

2007 Magna Cum Laude Honors in Chemistry, Cornell University

2008 American Heart Association Medical Student Research Fellowship

2011 Sarnoff Cardiovascular Research Fellowship: 1 Year Program at Massachusetts General Hospital

2015 Society For Vascular Surgery General Surgery Travel Scholarship

2015 Robert R. Linton Fellowship in Vascular Surgery

2015 Harvard-Longwood Vascular NIH T32 Training Grant - T32-HL 007734

2015 Wellcome Trust Foundation Selection for Advanced Course in Design and Analysis of Genetic-based Association Studies For Young Investigators

2015 Finalist at New England Society for Vascular Surgery Meeting for Best Abstract

2017 Finalist at New England Society for Vascular Surgery Meeting for Best Abstract

2017 Top 10% Poster Abstract Review Score at the American Society for Human Genetics Meeting

2018 Journal of Vascular Surgery Editor's Choice Manuscript: Risk Factor profile and anatomic features of previously asymptomatic patients presenting with carotid-related stroke

2019 Nature Medicine Manuscript Selection for 25th Anniversary Focus on Cardiometabolic Disease: Genome-wide association study of peripheral artery disease in the Million Veteran Program

2019 American Heart Association Top Heart Disease and Stroke Research Advances of 2019: Klarin D et al. "Genome-wide association analysis of venous thromboembolism identifies new risk loci and genetic overlap with arterial vascular disease." *Nat Genet*. 2019 Nov;51(11):1574-1579.

2019 American Heart Association Top Heart Disease and Stroke Research Advances of 2019: Klarin D et al. "Genome-wide association study of peripheral artery disease in the Million Veteran Program." *Nat Med*. 2019 Aug;25(8):1274-1279.

C. Contributions to Science

I have made the following scientific contributions.

1. **Genetic characterization of blood lipids in diverse populations identifies therapeutic targets for cardiovascular disease.** In the first large-scale genetic analysis from the Million Veteran program, we identified novel loci associated with plasma lipid concentrations with implications for cardiovascular therapy. Through a focus on mutations predicted to result in a loss of gene function, we showed that individuals who possess a damaging or loss of function mutation in the gene phosphodiesterase 3B, the target of the medicine cilostazol, demonstrate lower levels of plasma triglycerides and higher levels of HDL cholesterol. In addition, we demonstrated that loss of function mutations in *ANGPTL3* (Angiopoietin-like protein 3) were associated with atheroprotective plasma lipid profiles. These findings suggest that drug therapies targeting these genes may be appropriate for the primary or secondary prevention of coronary artery disease.

a. **Klarin D,** Damrauer SM, Cho K, Sun YV, Teslovich TM, Honerlaw J, Gagnon D, Duvall SL, Li J, Peloso GM, Chaffin M, Small AM, Huang J, Tang H, Lynch JA, Ho Y, Liu DJ, Emdin CA, Li AH, Huffman JE, Lee JS, Natarajan P, Chowdhury R, Saleheen D, Vujkovic M, Baras A, Pyarajan S, Di Angelantonio E, Neale BM, Naheed A, Khera AV, Danesh J, Chang KM, Abecasis G, Willer C, Dewey FE, Carey DJ, GLGC, MIGen Consortium, The Geisinger-Regeneron DiscovEHR Collaboration, The VA Million Veteran Program, Concato J, Gaziano JM, O'Donnell CJ, Tsao PS, Kathiresan S, Rader DJ, Wilson PWF, Assimes TL. "Genetics of blood lipids among ~300,000 multi-ethnic participants of the Million Veteran Program." Nat Genet. 2018 Nov;50(11):1514-1523.

b. Stitziel NO, Khera AV, Wang X, Bierhals AJ, Vourakis AC, Sperry AE, Natarajan P, **Klarin D**, Emdin CA, Zekavat SM, Nomura A, Erdmann J, Schunkert H, Samani NJ, Kraus WE, Shah SH, Yu B, Boerwinkle E, Rader DJ, Gupta N, Frossard PM, Rasheed A, Danesh J, Lander ES, Gabriel S, Saleheen D, Musunuru K, Kathiresan S; PROMIS and Myocardial Infarction Genetics Consortium Investigators. "ANGPTL3 Deficiency and Protection Against Coronary Disease." J Am Coll Cardiol. 2017 Apr 25;69(16):2054-2063.

2. Understanding the genetic architecture of atherosclerotic disease in the peripheral vasculature. Unlike most early work in atherosclerosis genomics that focused exclusively on coronary artery disease, I have led more recent large-scale efforts to characterize the genetics of vascular disease in the peripheral circulation. In the largest genetic analysis of peripheral artery disease (PAD) to-date, we identified 18 novel genetic associations, including four variants that appeared to be specific for PAD. The Factor V Leiden mutation (*F5* p.R506Q) was found to be uniquely associated with PAD, highlighting the pathogenic role of thrombosis in the peripheral vascular bed and providing genetic support for Factor Xa inhibition as a therapeutic strategy for PAD. Similar work on abdominal aortic aneurysms (AAA) highlighted AAA-lipid gene associations with therapeutic implications and using causal inference methods (Mendelian randomization) demonstrated that diastolic blood pressure - as opposed to systolic blood pressure - is likely of greater significance in the pathogenesis of AAA.

a. **Klarin D**, Lynch J, Aragam K, Chaffin M, Assimes TL, Huang J, Lee KM, Shao Q, Huffman JE, Natarajan P, Arya S, Small A, Sun YV, Vujkovic M, Freiberg MS, Wang L, Chen J, Saleheen D, Lee JS, Miller DR, Reaven P, Alba PR, Patterson OV, DuVall SL, Boden WE, Beckman JA, Gaziano JM, Concato J, Rader DJ, Cho K, Chang KM, Wilson PWF, O'Donnell CJ, Kathiresan S; VA Million Veteran Program, Tsao PS, Damrauer SM. "Genome-wide association study of peripheral artery disease in the Million Veteran Program." Nat Med. 2019 Aug;25(8):1274-1279.

b. **Klarin D**, Verma SS, Judy R, Dikilitas O, Wolford BN, Paranjpe I, Levin MG, Pan C, Tcheandjieu C, Spin JM, Lynch J, Assimes TL, Nyrønning LÅ, Mattsson E, Edwards TL, Denny J, Larson E, Lee MTM, Carrell D, Zhang Y, Jarvik GP, Gharavi AG, Harley J, Mentch F, Pacheco JA, Hakonarson H, Skogholt AH, Thomas L, Gabrielsen ME, Hveem K, Nielsen JB, Zhou W, Fritsche L, Huang J, Natarajan P, Sun YV, DuVall SL, Rader DJ, Cho K, Chang KM, Wilson PWF, O'Donnell CJ, Kathiresan S, Scali ST, Berceli SA, Willer C, Jones GT, Bown MJ, Nadkarni G, Kullo IJ, Ritchie M, Damrauer SM, Tsao PS. "Genetic Architecture of Abdominal Aortic Aneurysm in the Million Veteran Program." Circulation. 2020 Sep 28. doi: 10.1161/CIRCULATIONAHA.120.047544.

3. A polygenic risk score predicts incident disease events. Complementing my work in the arterial space, I have lead two large-scale biobank efforts examining venous thromboembolism disease risk across the human genome. In addition to the discovery of novel genetic associations, we found that venous thrombosis has a much stronger genetic correlation with PAD than with coronary artery disease or large artery stroke. We also developed a new polygenic risk score, or multi-gene profile of genetic risk, that identified 5% of the population at 2-3-fold higher incident venous thromboembolic risk. This was the first instance in which a polygenic risk score was observed to predict future/incident disease events in an at risk population. By leveraging individuals with high genetic risk for event enrichment and maximization of therapeutic efficacy, these results serve as a roadmap for polygenic risk score implementation in a clinical trial setting.

a. **Klarin D**, Busenkell E, Judy R, Lynch J, Levin M, Haessler J, Aragam K, Chaffin M, Haas M, Lindström S, Assimes T, Huang J, Lee KM, Shao Q, Huffman JE, Kabrhel C, Huang Y, Sun YV, Vujkovic M, Saleheen D, Miller DR, Reaven P, DuVall S, Boden WE, Pyarajan S, Reiner AP, Trégouët DA, Henke P, Kooperberg C, Gaziano JM, Concato J, Rader DJ, Cho K, Chang KM, Wilson PW, Smith NL, O'Donnell CJ, Tsao PS, Kathiresan S, Obi A, Damrauer SM, Natarajan P, INVENT Consortium, VA Million Veteran Program. "Genome-wide association analysis of venous thromboembolism identifies new risk loci and genetic overlap with arterial vascular disease." Nat Genet. 2019 Nov;51(11):1574-1579.

b. **Klarin D**, Emdin C, Natarajan P, Conrad MF, the INVENT consortium, Kathiresan S. "Genetic Analysis of Venous Thromboembolism in UK Biobank identifies the ZFPM2 locus and Implicates Obesity as a Causal Risk Factor." Circ Cardiovasc Genet. 2017 Apr;10(2). pii: e001643. doi: 10.1161/CIRCGENETICS.116.001643.

4. Transendothelial migration of leukocytes contributes to risk of coronary artery disease. In my initial work in atherosclerotic cardiovascular disease genetic analysis, we used an electronic health record-based approach to identify 15 new coronary artery disease risk-gene associations. Through phenome-scanning and additional secondary analysis, we demonstrated one of these genetic loci, *CCDC92,* likely acts through insulin resistance pathways. In addition, *in vitro* analysis of the *ARHGEF26* p.V29L coronary artery disease risk mutation provided human genetic support for a role for the transendothelial migration of leukocytes as a key step in the formation of atherosclerosis.

a. **Klarin D**, Zhu QM, Emdin CA, Chaffin M, Horner S, McMillan BJ, Leed A, Weale ME, Spencer CCA, Aguet F, Segrè AV, Ardlie KG, Khera AV, Natarajan P, Kaushik VK, CARDIoGRAMplusC4D Consortium, Kathiresan S. "Genetic analysis in UK Biobank links insulin resistance and transendothelial migration pathways to coronary artery disease." Nat Genet. 2017 Sep;49(9):1392-1397

5. Determinants of stroke risk following among individuals with severe atherosclerotic phenotypes. By leveraging single institution and national registry data, we identified significant determinants of perioperative stroke among individuals with hemodynamically significant carotid stenosis. First, we observed that a large proportion (43%) of previously asymptomatic individuals who presented with a first-time stroke event were noted to have an occluded culprit carotid artery, a hallmark of severe atherosclerosis and making them ineligible for subsequent carotid revascularization. In addition, we found that well-selected individuals with severe chronic kidney disease, despite their significant atherosclerotic burden, could safely undergo carotid revascularization with low rates of perioperative stroke and mortality. Lastly, among individuals with atherosclerosis in both the coronary and carotid vascular beds, concomitant coronary and carotid revascularization was not shown to reduce perioperative stroke risk.

a. **Klarin D**, Lancaster RT, Ergul E, Bertges D, Goodney P, Schermerhorn ML, Cambria RP, Patel VI, Vascular Study Group of New England. "Perioperative and long-term impact of chronic kidney disease on carotid artery interventions." J Vasc Surg. 2016 Nov;64(5):1295-1302.

b. **Klarin D**, Cambria RP, Ergul EA, Silverman SB, Patel VI, LaMuraglia GM, Conrad MF, Clouse WD. "Risk factor profile and anatomic features of previously asymptomatic patients presenting with carotid-related stroke." J Vasc Surg. 2018 Nov;68(5):1390-1395.

c. **Klarin D**, Patel VI, Zhang S, Xian Y, Kosinski A, Yerokun B, Badhwar V, Thourani VH, Sundt TM, Shahian D, Melnitchouk S. "Concomitant carotid endarterectomy and cardiac surgery does not decrease postoperative stroke rates." J Vasc Surg. 2020 Feb 14. pii: S0741-5214(19)32591-1.

Complete List of Published Work in MyBibliography
https://www.ncbi.nlm.nih.gov/myncbi/1zq4aerOhc5oik/bibliography/public/

D. Additional Information: Research Support and/or Scholastic Performance

Completed Research Support

5T32HL007734 LoGerfo(PI) 07/01/15-06/30/17
NHLBI/NIH
Harvard Longwood T32 in Vascular Surgery
This training grant provides salary support for research fellows in general surgery pursuing subspecialty training in vascular surgery to perform scientific research directly applicable to a career as a surgeon-scientist.
Role: Trainee