“Diabetes now represents ~10% of the US population and prediabetes looms 5-8 times more prevalent. The historic simple classification has been gestational diabetes which often but not always remits after pregnancy, type 1 diabetes (autoimmune, 5-10%) and type 2 diabetes (insulin resistance with progressive beta cell failure). In this update using soft clustering analysis of genetic loci associated with type 2 diabetes, classification of patients into 5 groups was based on biologically-supported mechanisms. For the clinician I wish this were more simple but for the scientist it’s clearly more exciting.”

Type 2 diabetes genetic loci informed by multi-trait associations point to disease mechanisms and subtypes: A soft clustering analysis.

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BACKGROUND:
Type 2 diabetes (T2D) is a heterogeneous disease for which (1) disease-causing pathways are incompletely understood and (2) subclassification may improve patient management. Unlike other biomarkers, germline genetic markers do not change with disease progression or treatment. In this paper, we test whether a germline genetic approach informed by physiology can be used to deconstruct T2D heterogeneity. First, we aimed to categorize genetic loci into groups representing likely disease mechanistic pathways. Second, we asked whether the novel clusters of genetic loci we identified have any broad clinical consequence, as assessed in four separate subsets of individuals with T2D.

METHODS AND FINDINGS:
In an effort to identify mechanistic pathways driven by established T2D genetic loci, we applied Bayesian nonnegative matrix factorization (bNMF) clustering to genome-wide association study (GWAS) results for 94 independent T2D genetic variants and 47 diabetes-related traits. We identified five robust clusters of T2D loci and traits, each with distinct tissue-specific enhancer enrichment based on analysis of epigenomic data from 28 cell types. Two clusters contained variant-trait associations indicative of reduced beta cell function, differing from each other by high versus low proinsulin levels. The three other clusters displayed features of insulin resistance: obesity mediated (high body mass index [BMI] and waist circumference [WC]), ”lipodystrophy-like” fat distribution (low BMI, adiponectin, and high-density lipoprotein [HDL] cholesterol, and high triglycerides), and disrupted liver lipid metabolism (low triglycerides). Increased cluster genetic risk scores were associated with distinct clinical outcomes, including increased blood pressure, coronary artery disease (CAD), and stroke. We evaluated the potential for clinical impact of these clusters in four studies containing individuals with T2D (Metabolic Syndrome in Men Study [METSIM], N = 487; Ashkenazi, N = 509; Partners Biobank, N = 2,065; UK Biobank [UKBB], N = 14,813). Individuals with T2D in the top genetic risk score decile for each cluster reproducibly exhibited the predicted cluster-associated phenotypes, with approximately 30% of all individuals assigned to just one cluster top decile. Limitations of this study include that the genetic variants used in the cluster analysis were restricted to those associated with T2D in populations of European ancestry.

CONCLUSION:
Our approach identifies salient T2D genetically anchored and physiologically informed pathways, and supports the use of genetics to deconstruct T2D heterogeneity. Classification of patients by these genetic pathways may offer a step toward genetically informed T2D patient management.
RESEARCH CORNER

Dr. Dana Dabelea, MD., PhD. is a Professor of Epidemiology and Pediatrics and the Director of the Lifecourse Epidemiology of Adiposity and Diabetes (LEAD) Center at the University of Colorado Anschutz Medical Campus (AMC). Her main research interest is understanding how early life behaviors, environmental exposures and other risk factors operating during fetal or early post-natal life, influence the development of obesity, diabetes and cardiovascular outcomes throughout the lifecourse (developmental origins of health and disease). Her experience includes epidemiological studies with community-based and clinic-based sampling, longitudinal follow-up and extensive sample collection and storage. As the Director of the LEAD Center and lead investigator on over $18 million NIH and CDC grants, she oversees large, longitudinal, cohort studies spanning the entire lifecourse, from pregnancy through old age. Among others, she serves as national Co-Chair of the Steering Committee for the multi-center SEARCH for Diabetes in Youth Study. SEARCH is a landmark US population-based study conducting both surveillance and observational research in the field of pediatric type 1 and type 2 diabetes. Dr. Dabelea is also part of the Diabetes Prevention Program Outcomes Study (DPPOS), another landmark US diabetes study in older adults, which has provided the evidence base for diabetes prevention efforts, and is now studying diabetes-and aging-related outcomes and comorbidities. Finally, Dr. Dabelea is also Principal Investigator of Healthy Start, a Colorado pre-birth cohort study following over 1400 mother–child dyads from before birth through childhood and adolescence, to understand the developmental origins of several chronic pediatric diseases. With Healthy Start, Dr. Dabelea leads a multi-disciplinary team of investigators at the AMC and Colorado State University (CSU), as part of the NIH-assembled ECHO consortium (Environmental influences on Childhood Health Outcomes). These studies, several ancillary studies supported by these cohorts, as well as other studies conducted by LEAD investigators under Dr. Dabelea’s direction, provide an exceptionally rich resource for training and mentoring students, junior faculty, residents and fellows in clinical diabetes research, lifecourse research, maternal and child health research, and chronic disease epidemiology.

THE CENTER FOR BIOETHICS

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The Center for Bioethics and the Humanities at CU is poised to become one of the nation’s leading empirical research centers in bioethics and the health humanities, following the recruitment of Dr. Eric Campbell to lead the effort. Dr. Campbell joined CU in April 2018 from The Massachusetts General Hospital and Harvard Medical School where he was Professor of Medicine, Associate Director of the Mongan Institute for Health Policy and the Director of Research at the Center for Bioethics at Harvard Medical School.

The Center’s aggressive agenda in empirical research includes hiring new faculty, creating a post-doctoral program, exploring doctoral training tracks, and stimulating novel research by providing pilot funding to support new grant applications. According to Dr. Campbell: “Our goal is to create a world-class empirical bioethics and humanities research organization at CU, grounded in the traditional model of extramural research support, publications in high impact journals, presentations at major professional meetings and appearances in the national media. The leadership of CU has generously provided us with the resources to make this happen and we need to be good stewards of those resources in the relentless pursuit of this goal.”

About Dr. Campbell

Eric G. Campbell, PhD, is a health policy researcher with expertise in survey science who conducts research on conflicts of interest, medical professionalism, research misconduct and other topics at the intersection of health care policy and bioethics. Dr. Campbell has been continuously funded by numerous R01 awards from the National Institutes of Health and grants from private foundations. He has published 107 original research articles over his career, including 8 in the New England Journal of Medicine and 14 in the Journal of the American Medical Association. Dr. Campbell has twice testified before the United States Congress. He is a leading figure in the media at both the state and national levels, and in 2012 he received Health Services Research Impact award from AcademyHealth.