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Unveiling the Genetic Heterogeneity of Type 2 Diabetes: From Multi-ethnic Studies to Personalized Medicine

Mengting Luo
Institute of Life Science, Jiyang College of Zhejiang A&F University, Zhuji, 311800, China
Corresponding author email: juliemtluo@gmail.com

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The paper titled “Genetic drivers of heterogeneity in type 2 diabetes pathophysiology” published in Nature on February 19, 2024, authored by Ken Suzuki, Konstantinos Hatzikotoulas, Lorraine Southam, Henry J. Taylor, Xianyong Yin, Kim M. Lorenz, Ravi Mandla, et al., originates from institutions including the University of Manchester, UK, and the University of Tokyo, Japan. The study amalgamated genome-wide association study (GWAS) data from 2,535,601 individuals, 39.7% of whom were of non-European descent, including 428,452 cases of type 2 diabetes (T2D), aiming to characterize the genetic contributions to the development of T2D. It identified 1,289 independent association signals mapped to 611 loci, with 145 being novel discoveries. By defining cluster-based polygenic risk scores and examining their association with vascular outcomes related to T2D, the study highlighted the significant role of obesity-related processes in the development of vascular outcomes. Integrating and analyzing large-scale, multi-ethnic GWAS data, the study substantially expanded our understanding of the genetic diversity of T2D. Its results not only enhance our knowledge of the genetic architecture of T2D but also provide new directions for future research, especially in the development of customized treatment plans for T2D patients with specific genetic backgrounds. The findings of this study signify a step towards more personalized care for diabetes, emphasizing the importance of considering genetic heterogeneity in public health strategies and therapeutic interventions.

1 Experimental Data Analysis

This study has successfully identified 1,289 independent signals closely associated with Type 2 Diabetes (T2D), distributed across 611 genetic loci and encompassing a diverse range of ethnicities, including non-European ancestries. This underscores the importance of conducting genetic research in globally diverse populations. The integration with single-cell epigenomic data has provided deeper insights into the genetic diversity and complexity underlying T2D. These findings not only offer a new perspective on the genetic mechanisms driving T2D but also direct future research, particularly in the exploration of personalized treatment and management strategies, demonstrating the substantial potential of precision medicine.

Figure 1 presents a heatmap of the associations between 37 cardiometabolic phenotypes and 8 clusters of index SNVs related to T2D. Each column corresponds to a cluster, and each row corresponds to a cardiometabolic phenotype. The 'temperature' of each cell in the heatmap indicates the association's z-score for the phenotype with index SNVs assigned to a specific cluster (adjusted for the T2D risk allele). For instance, glucose-related phenotypes (such as fasting glucose and glycated hemoglobin) show a strong positive correlation with the "Beta cell +PI" and "Beta cell -PI" clusters, while showing a negative correlation with the "Obesity" cluster. After adjusting for body mass index, a complex relationship between different metabolic phenotypes and genetic pathways in the development of T2D is observed, which is essential for understanding the etiology of T2D and its interaction with cardiometabolic states.

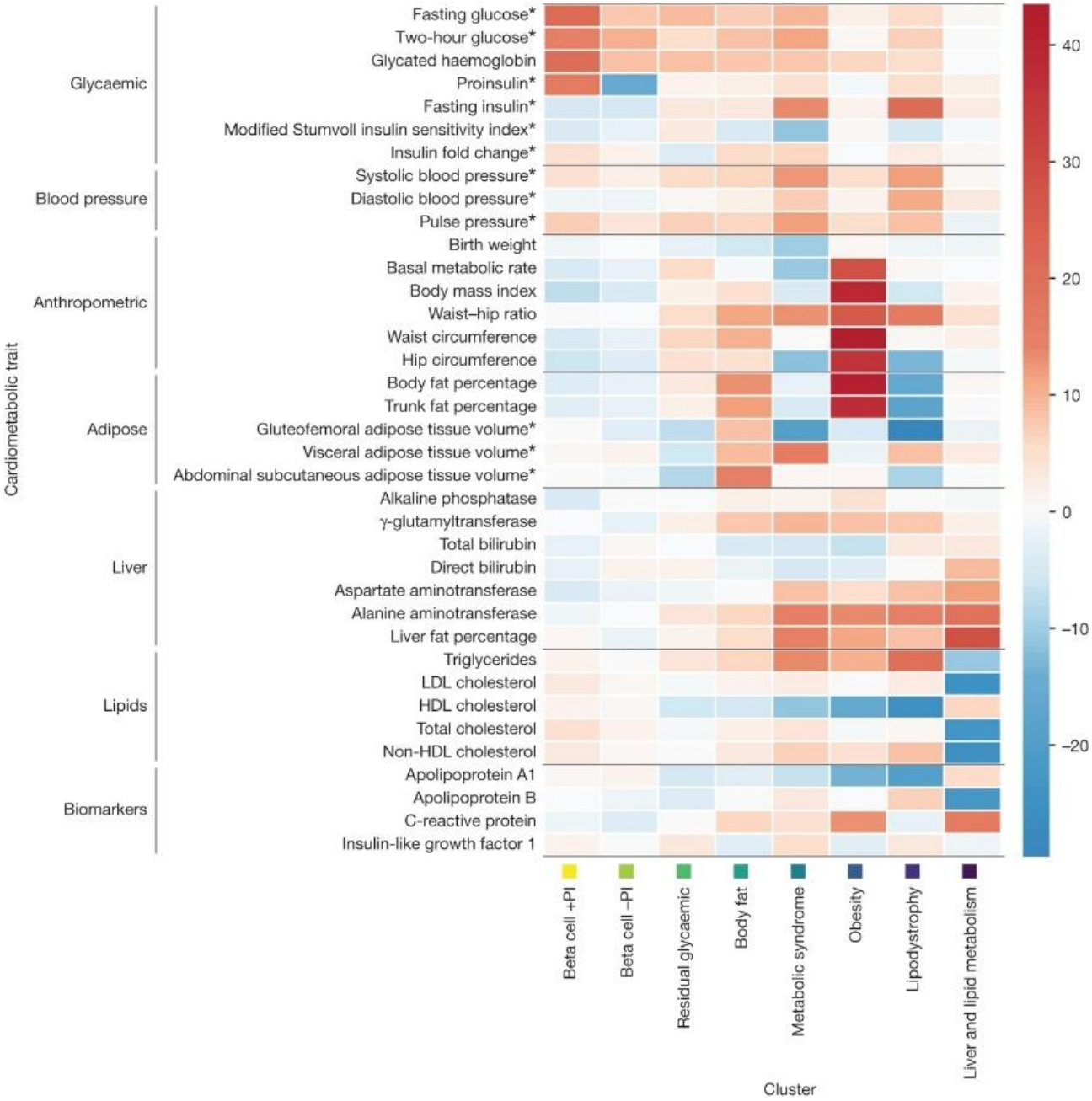

Figure 1 Heat map of associations of 37 cardiometabolic phenotypes with 8 mechanistic clusters of index SNVs for T2D association signals

Table 1 summarizes the cardiometabolic characteristics, example loci, and physiological effects of index SNV signals related to Type 2 Diabetes (T2D) across eight mechanistic clusters. For instance, the "Beta cell +PI" cluster is associated with increased fasting glucose, two-hour glucose, glycated hemoglobin, and proinsulin levels, but does not affect insulin secretion, influencing insulin sensitivity instead. Conversely, the "Obesity" cluster is related to an increase in body mass index (BMI), waist-hip ratio, body fat, and basal metabolic rate, but it is linked to a decrease in high-density lipoprotein (HDL) cholesterol levels. These clusters reveal the impact of specific genetic loci on T2D risk phenotypes, indicating that the development of T2D is associated with various metabolic pathways, each potentially driven by different genetic variations. These findings contribute to unveiling the complex genetic and metabolic network underlying T2D and provide potential targets for future treatments.

Table 1 Cardiometabolic profile, example loci and physiological effect of index SNVs at T2D association signals allocated to eight mechanistic clusters

Mechanistic cluster	Cardiometabolic profile	Number of T2D associations	Example loci	Physiological effect	
				Insulin secretion	Insulin sensitivity
Beta cell +PI	+FG*, +2hG*, +HbA1c, +PI*	91	*TCF7L2, KCNQ1, CDKAL1, CDKN2A–CDKN2B, SLC30A8*	–	+
Beta cell −PI	+FG*, +2hG*, +HbA1c, −PI*	89	*CDC123–CAMK1D, HNF1B, KCNJ11–ABCC8, HNF4A, HNF1A*	–	+
Residual glycaemic	+FG*, +HbA1c	389	*GCC1–PAX4–LEP, ANKRD55, GCKR, UBE2E2*	–	–
Body fat	+Body fat, +ASAT*	273	*ZMIZ1, HMGA2, CTBP1*	+	–
Metabolic syndrome	+FG*, +FI*, +WHR, +VAT*, −GFAT*, +TG, −HDL, +BP	166	*IGF2BP2, CCND2, HHEX–IDE, JAZF1, GPSM1*	+	–
Obesity	+BMI, +WHR, +body fat, +BMR, +TG, −HDL	233	*FTO, MC4R, MACF1, TMEM18*	+	–
Lipodystrophy	+FI*, +WHR, −body fat, −GFAT*, +TG, −HDL, +BP	45	*IRS1, GRB14–COBLL1, PPARG*	+	–
Liver and lipid metabolism	−LDL, −TC, +liver fat, +liver biomarkers	3	*TOMM40–APOE–GIPR, TM6SF2, PNPLA3*	–	–

Figure 2 presents a heatmap based on single-cell ATAC-seq peak values indicating regions of open chromatin associated with Type 2 Diabetes (T2D). Panels a and b respectively show 222 cell types from 30 adult and 15 fetal tissues, and 106 cell types from the human brain. The columns of the heatmap correspond to different mechanistic clusters, and the rows correspond to cell types. The 'temperature' of each cell indicates the logarithm of the fold enrichment for T2D association. Rows marked with an asterisk signify cell types that show significant enrichment for T2D association within at least one cluster (after Bonferroni correction). For instance, islet cells and certain cell types in the nervous system display open chromatin areas significantly associated with T2D, potentially offering insights into the cell-specific genetic regulation of T2D.

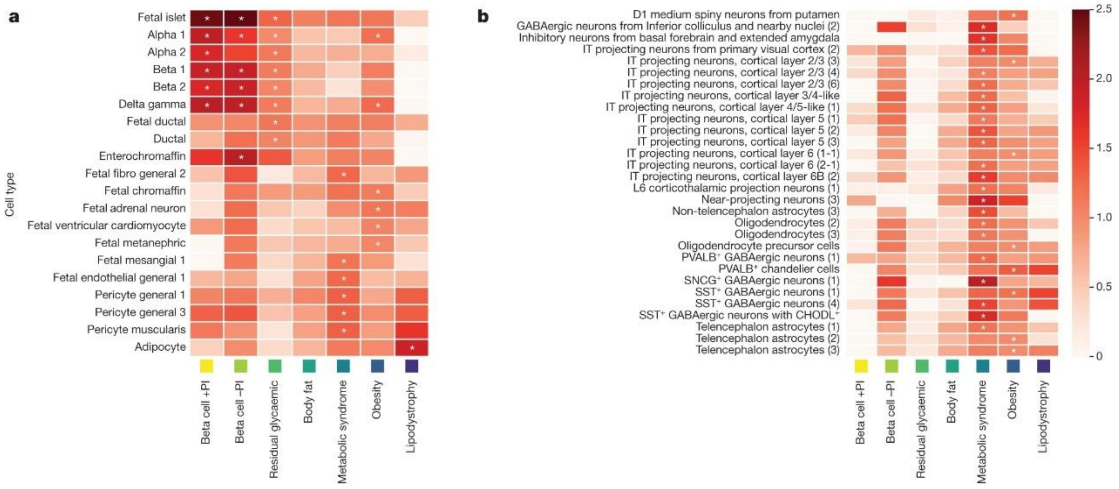

Figure 2 Heat map of cluster-specific enrichments of T2D associations for cell-type-specific regions of open chromatin derived from single-cell ATAC-seq peaks in adult and fetal tissue

Figure 3 shows the associations between cluster-specific components of partitioned polygenic scores (PS) and five vascular outcomes related to Type 2 Diabetes (T2D) across a cohort of 279,552 individuals from multiple ethnic

groups. The height of each bar represents the log-odds ratio (beta) of the cluster's association with a specific vascular outcome, with the grey bars indicating the 95% confidence intervals. Notably, the "Beta cell +PI" cluster exhibits a significant negative correlation with Coronary Artery Disease (CAD), while the "Obesity" cluster demonstrates a significant positive correlation with both CAD and Peripheral Artery Disease (PAD), suggesting a close relationship between different pathological processes related to T2D and the risk of specific vascular complications. These results underscore the importance of personalized treatment approaches targeting specific pathological processes in the management of T2D. An asterisk (*) indicates a nominal association with a P value less than 0.05, and a double asterisk (**) indicates a significant association after Bonferroni correction with a P value less than 0.0063.

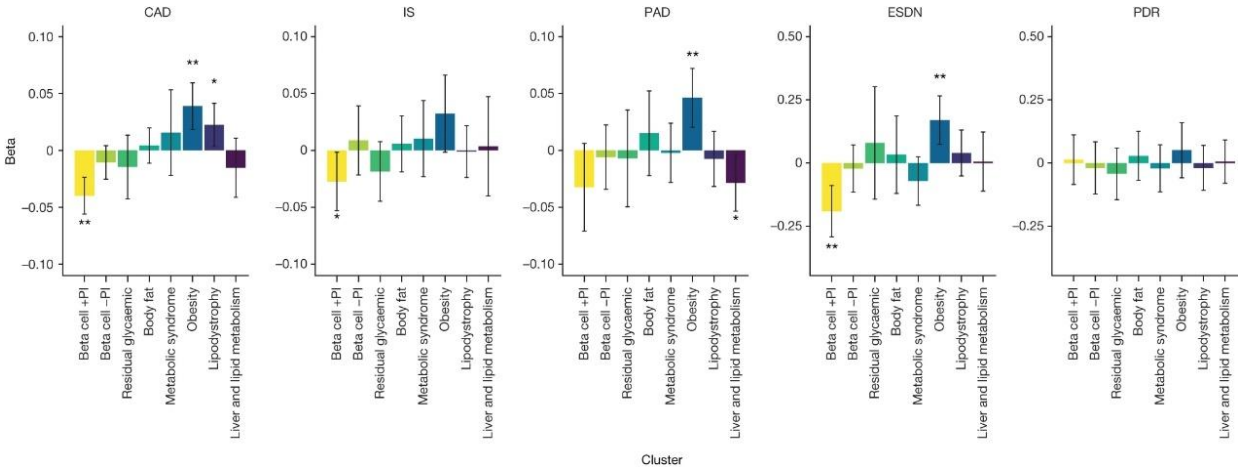

Figure 3 Associations of cluster-specific components of the partitioned PS with five T2D-related vascular outcomes in up to 279,552 individuals from multiple ancestry groups

2 Analysis of Research Findings

This study, through the construction of cluster-specific polygenic scores (PS), delves into the association between various clusters and vascular complications related to Type 2 Diabetes (T2D). The findings reveal a significant positive correlation between the genetic risk scores of the obesity cluster and conditions such as Coronary Artery Disease (CAD) and Peripheral Artery Disease (PAD), suggesting a pivotal role of obesity in the development of these vascular complications. Moreover, clusters associated with insulin secretion showed a negative correlation with CAD, potentially reflecting the role of impaired insulin secretion in cardiovascular risk. These analytical results highlight the diverse roles of different genetic clusters in the risk of T2D complications, providing vital information for personalized diabetes care and aiding the design of more precise treatment strategies in the future. Integrating global genetic information can guide treatment decisions more effectively, especially in the prevention and management of vascular complications in T2D patients. This method of risk assessment based on genetic clusters paves new paths for the optimization of diabetes care globally.

3 Evaluation of the Research

This study conducted an in-depth analysis of the genetic heterogeneity of Type 2 Diabetes (T2D) by integrating genome-wide association data from multiple ethnic groups with single-cell epigenetic data, demonstrating the potential of big data in deciphering the complex genetic backdrop of diseases. The unique analytical framework proposed by this research offers new methodologies for identifying and understanding the risk factors for T2D across diverse genetic backgrounds, advancing the application of personalized medicine in diabetes management. However, the study's capture of global genetic diversity is not yet comprehensive, particularly lacking data from regions such as Africa, South America, and the Middle East, which limits the universality of its findings. Future research needs to expand the sample size to more fully reveal the genetic mechanisms of T2D.

4 Conclusion

This study has provided unprecedented insights into the genetic heterogeneity of Type 2 Diabetes, particularly highlighting the central role of obesity in the development of the disease. Its findings offer valuable genetic

information for personalized treatment strategies and present new approaches for the prevention and management of diabetes on a global scale, contributing to the advancement of more effective disease intervention measures.

5 Access the Full Text

Suzuki, K., Hatzikotoulas, K., Southam, L. et al. Genetic drivers of heterogeneity in type 2 diabetes pathophysiology. Nature 627, 347–357 (2024). https://doi.org/10.1038/s41586-024-07019-6

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