applied sciences

MDPI

Communication

Enrichment of Spatial eGenes Colocalized with Type 2 Diabetes Mellitus Genome-Wide Association Study Signals in the Lysosomal Pathway

Younyoung Kim and Chaeyoung Lee *

School of Systems Biomedical Science and Integrative Institute of Basic Science, Soongsil University, 369 Sangdo-ro, Dongjak-gu, Seoul 06978, Republic of Korea
* Correspondence: clee@ssu.ac.kr; Tel.: +82-2-820-0455

Abstract: Genome-wide association studies (GWAS) have identified genetic markers associated with type 2 diabetes mellitus (T2DM). Additionally, tissue-specific expression quantitative trait loci (eQTL) studies have revealed regulatory elements influencing gene expression in specific tissues. We performed enrichment analyses using spatial eGenes corresponding to known T2DM GWAS signals to uncover T2DM pathological pathways. T2DM GWAS signals were obtained from the GWAS Catalog, and spatial eQTL data from T2DM-associated tissues, including visceral adipose tissue, liver, skeletal muscle, and pancreas, were sourced from the Genotype-Tissue Expression Consortium. The eGenes were enriched in Kyoto Encyclopedia of Genes and Genomes biological pathways using the Benjamini–Hochberg method. Colocalization analysis of 2857 independent T2DM GWAS signals identified 556 eGenes in visceral adipose tissue, 176 in liver, 715 in skeletal muscle, and 384 in pancreas ($P_{FDR} < 0.05$ where P_{FDR} is the false discovery rate). These eGenes showed enrichment in various pathways ($P_{BH} < 0.05$ where P_{BH} is the corrected P for the Benjamini–Hochberg multiple testing), especially the lysosomal pathway in pancreatic tissue. Unlike the mTOR pathway in T2DM autophagy dysregulation, the role of lysosomes remains poorly understood. The enrichment analysis of spatial eGenes associated with T2DM GWAS signals highlights the importance of the lysosomal pathway in autophagic termination. Thus, investigating the processes involving autophagic termination associated with lysosomes is a priority for understanding T2DM pathogenesis.

Keywords: autophagy; enrichment analysis; expression gene; lysosome; type 2 diabetes

check for updates

Citation: Kim, Y.; Lee, C. Enrichment of Spatial eGenes Colocalized with Type 2 Diabetes Mellitus Genome-Wide Association Study Signals in the Lysosomal Pathway. *Appl. Sci.* **2023**, *13*, 10447. https://doi.org/10.3390/app131810447

Academic Editor: Dirk Tischler

Received: 27 July 2023
Revised: 8 September 2023
Accepted: 15 September 2023
Published: 19 September 2023

Copyright: © 2023 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/).

1. Introduction

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disease that can significantly impact daily life and result in severe complications. It is characterized by elevated levels of plasma glucose due to impaired glucose metabolism, insulin resistance, and impaired insulin secretion. The dysregulation of glucose homeostasis, leading to T2DM, can be attributed to various mechanisms such as reduced peripheral glucose uptake in muscles, cytokine secretion in adipose tissue, increased glucose production in the liver, impaired insulin secretion in the pancreas, and neuroendocrine regulation by the central nervous system [1]. Hyperglycemia, a hallmark of T2DM, can lead to the overproduction of reactive oxygen species (ROS), causing oxidative stress and redox imbalance, which is a major contributor to the etiology of T2DM [2].

Extensive research efforts have been directed towards understanding the genetic susceptibility to T2DM. In particular, genome-wide association studies (GWAS) have been extensively conducted over the past 15 years, moving away from the limited scope of linkage analysis that only identified genetic variants segregating within families. These GWAS studies have made significant contributions to the identification of common genetic factors associated with T2DM. The findings from these studies provide valuable insights into the pathological pathways involved in the development of T2DM. For instance, rs13266634,

previously identified in studies by Sladek et al. [3], Zeggini et al. [4], and Scott et al. [5], is an exonic variant of SLC30A8. This variant creates an R to W missense mutation at position 325 in the β-cell zinc transporter ZnT-8, which plays a crucial role in the final biosynthetic pathway of insulin production and secretion [6,7]. However, the precise contributions of many GWAS signals to T2DM susceptibility remain unclear, as they are often located in intergenic regions, and their target genes are assigned physically close to these signals. To address this challenge, researchers have explored expression quantitative trait loci (eQTLs) and their corresponding target genes (eGenes). An example of this approach is the identification of 33 eGenes through the integration of 143 meta-GWAS signals with gene expression data from blood samples [8]. Nonetheless, our understanding of the functional roles of eGenes remains limited, as their association with T2DM does not necessarily indicate that a particular tissue is implicated in T2DM development. Recent eQTL studies have focused on tissue-specific eQTL-eGene associations. For instance, a study examining eQTLs specific to skeletal muscle revealed an eQTL (rs4547172; $p < 1.96 \times 10^{-5}$) of *PFKM*, a critical regulatory enzyme of glycolysis [9]. This eQTL was found to be in linkage with a T2DM GWAS signal (rs11168327; $p = 2.7 \times 10^{-3}$) identified by the DIAGRAM consortium [10]. Furthermore, based on the additional association of this eQTL with glucose uptake in skeletal muscle ($p = 0.016$), *PFKM* has been proposed as a potential factor involved in the regulation of insulin sensitivity in skeletal muscle cells. Another association study of T2DM with genes encoding glutathione-metabolizing enzymes (GSS and GGT7) identified nucleotide variants (rs13041792, rs6119534, and rs11546155; $p < 0.05$) in linkage to eQTLs associated ($p < 0.05$) with the pancreatic expression of genes (MAP1LC3A, EDEM2, MYH7B, and CPNE1) involved in the unfolded protein response pathway [11]. This study suggests a hypothesis that glutathione deficiency may contribute to misfolded proinsulin, leading to apoptosis of pancreatic beta cells. Other tissue-specific eQTL studies have indicated additional etiological factors in T2DM, such as metabolic stress-induced beta cell dysfunction [12] and mitochondrial dysfunction in adipose tissue [13]. The objective of this study was to identify spatial eGenes associated with T2DM GWAS signals and conduct enrichment analysis on these eGenes to uncover pathological pathways potentially contributing to the development of T2DM.

2. Materials and Methods

2.1. Colocalization Analysis

To examine the colocalization of single nucleotide variants associated with T2DM susceptibility in GWAS, we analyzed their relationship with spatial eQTLs in visceral adipose tissue, liver, skeletal muscle, and pancreas. These tissues were selected because T2DM is primarily caused by insulin resistance in visceral adipose tissue, liver, and skeletal muscle, followed by impaired insulin secretion by pancreatic β-cells to overcome the insulin resistance [14]. GWAS signals were obtained from the National Human Genome Research Institute-European Bioinformatics Institute GWAS Catalog (https://www.ebi.ac.uk/gwas; accessed on 10 June 2021). The GWAS signals analyzed in this study have shown suggestive associations with the significance threshold of p-value = 1×10^{-5} empirically estimated for GWAS by Hindorff et al. [15]. The experimental factor ontology identifier of T2DM used in the current study was MONDO_0005148. Only independent signals were selected for colocalization. The colocalization for the T2DM GWAS signals was found when the representative nucleotide variant within each signal was matched or strongly linked ($r^2 > 0.95$) to any eQTL provided by the Genotype-Tissue Expression (GTEx) Consortium [16]. A file including summary statistics for eQTL-eGene associations was downloaded for each tissue (v8; https://gtexportal.org; accessed on 20 June 2021). The summary statistics were estimated by the FastQTL [17], a linear regression program to find the best nominal association between gene expression levels and genotypes. Of course, the gene expression levels were preliminary filtered and normalized by the consortium (for details, see the article by the GTEx Consortium [16]). Statistical significance for colocalization in the current study was determined by 5% false discovery rate (P_{FDR}) per tissue.

2.2. Enrichment Analysis

We investigated the enrichment of eGenes identified from the colocalization analysis with T2DM GWAS signals in each of the Kyoto Encyclopedia of Genes and Genomes (KEGG) biological pathway terms using Enrichr (https://maayanlab.cloud/Enrichr; accessed on 15 July 2021) [18]. The KEGG pathways included genetic and environmental information processes, cellular processes, metabolism, organismal systems, human diseases, and drug development. Enrichment analyses were conducted with eGenes specific to each tissue, and further with eGenes shared by two or more tissues. The significance threshold for enrichment was set at $P_{BH} = 0.05$ where P_{BH} is the p-value adjusted for the Benjamini–Hochberg multiple testing.

This study was exempt from IRB review because we used publicly available population-based secondary data and subjects could not be identified.

3. Results

3.1. Colocalization Analysis

In the GWAS Catalog, we identified a total of 4049 genetic associations of single nucleotide variants with T2DM susceptibility ($p < 10^{-5}$). After excluding duplicates, 2857 unique GWAS signals remained. All available GWAS signal-eQTL pairs were searched to see if they were colocalized. This colocalization analysis revealed 556 eGenes for visceral adipose tissue, 176 eGenes for the liver, 715 eGenes for skeletal muscle, and 384 eGenes for the pancreas ($P_{FDR} < 0.05$; Figure 1). The numbers of eGenes shared by multiple tissues are also presented in Figure 1.

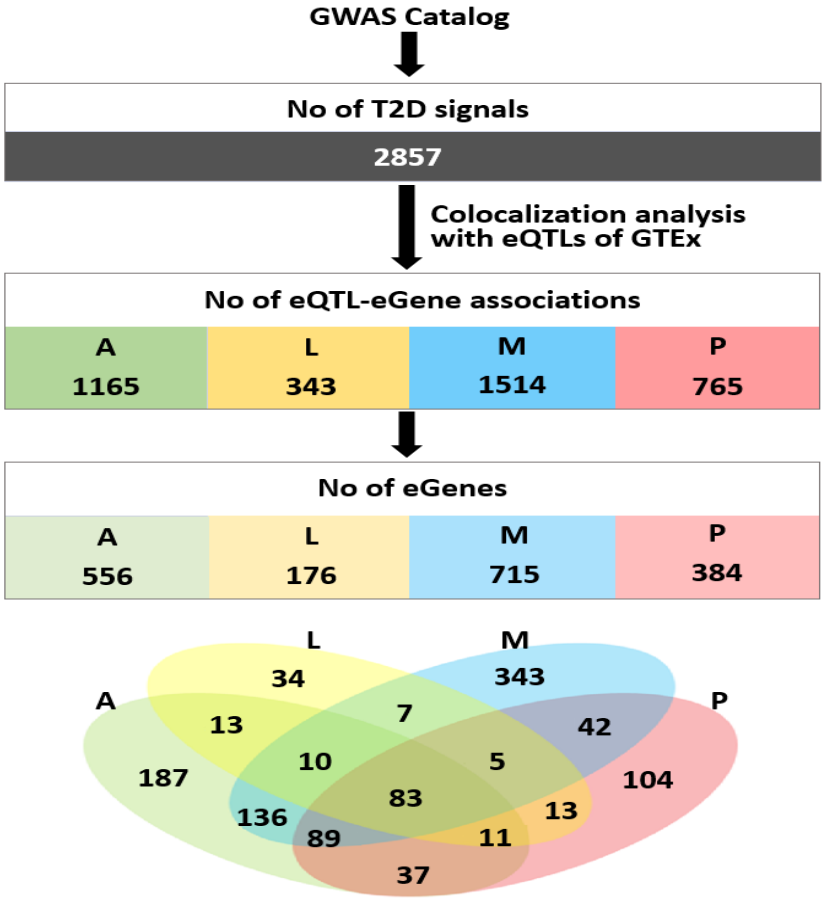

Figure 1. Number of eGenes targeting etiology of T2DM by its relevant tissues. A: visceral adipose tissue, L: liver, M: skeletal muscle, P: pancreas.

3.2. Enrichment Analysis

Enrichment analysis showed that these eGenes were significantly enriched in 12 pathways for visceral adipose tissue, 18 pathways for the liver, 22 pathways for skeletal muscle, and 20 pathways for the pancreas ($P_{BH} < 0.05$; Supplementary Tables S1–S4). None of these enriched pathways were identified when analyzing the mapped genes physically close to T2DM GWAS signals (Supplementary Table S5). Except for major histocompatibility complex (MHC)-related pathways, only two pathways were found to be enriched: 'lysosome' for the pancreas and 'other glycan degradation' for skeletal muscle. Subsequent enrichment analysis was performed to investigate whether the eGenes shared by multiple tissues were enriched in these two pathways (Tables 1 and 2). In particular, the eGenes shared by the the pancreas and skeletal muscle showed the largest enrichment in the term 'lysosome' ($P_{BH} = 1.1 \times 10^{-3}$).

Table 1. Enrichment of 'lysosome'-related eGenes resulted from T2DM GWAS signals.

Tissue [a]	eGenes Relevant to Lysosome		*p*-Value [c]	
	Name	No [b]	Raw	Adjusted [d]
A	GGA3, NPC1, IDUA, HYAL3, CTSH, CTSW, AP3S2, AP3B2	8	**2.9×10^{-2}**	3.2×10^{-1}
L	CTSH, AP3S2, ABCB9	3	1.0×10^{-1}	4.3×10^{-1}
M	NPC1, IDUA, CTSZ, HYAL3, GBA, CTSH, ACP2, AP3S2, DNASE2, ABCB9, AP3B2	11	**6.2×10^{-3}**	7.1×10^{-2}
P	NPC1, IDUA, HYAL3, GBA, CTSH, AP3S2, ABCB9, AP3B2	8	**3.3×10^{-3}**	**4.0×10^{-2}**
AL	CTSH, AP3S2	2	1.7×10^{-1}	4.1×10^{-1}
AM	NPC1, IDUA, HYAL3, CTSH, AP3S2, AP3B2	6	1.7×10^{-2}	1.2×10^{-1}
AP	NPC1, IDUA, HYAL3, CTSH, AP3S2, AP3B2	6	**2.9×10^{-3}**	**1.8×10^{-2}**
LM	CTSH, AP3S2, ABCB9	3	**3.0×10^{-2}**	8.9×10^{-2}
LP	CTSH, AP3S2, ABCB9	3	**3.5×10^{-2}**	1.1×10^{-1}
MP	NPC1, IDUA, HYAL3, GBA, CTSH, AP3S2, ABCB9, AP3B2	8	**8.4×10^{-5}**	**1.1×10^{-3}**
ALM	CTSH, AP3S2	2	1.2×10^{-1}	2.5×10^{-1}
ALP	CTSH, AP3S2	2	1.2×10^{-1}	2.7×10^{-1}
AMP	NPC1, IDUA, HYAL3, CTSH, AP3S2, AP3B2	6	**8.5×10^{-4}**	**4.7×10^{-3}**
LMP	CTSH, AP3S2, ABCB9	3	**1.9×10^{-2}**	5.1×10^{-2}
ALMP	CTSH, AP3S2	2	9.9×10^{-2}	2.0×10^{-1}

[a] Two or more letters indicate that enrichment was analyzed using eGenes shared by tissues. A: visceral adipose tissue; L: liver; M: skeletal muscle; P: pancreas. [b] There was a total of 128 lysosome-related genes in the KEGG pathway. [c] Significance with $p < 0.05$ is presented in bold. [d] Adjusted *p*-values were obtained using the Benjamini–Hochberg method to correct for multiple testing.

Table 2. Enrichment of 'other glycan degradation'-related eGenes resulted from T2DM GWAS signals.

Tissue [a]	eGenes Relevant to Other Glycan Degradation		*p*-Value [c]	
	Name	No [b]	Raw	Adjusted [d]
A	MAN2C1, GBA2	2	9.1×10^{-2}	8.0×10^{-1}
L	MAN2C1	1	1.5×10^{-1}	5.7×10^{-1}

Table 2. *Cont.*

Tissue [a]	eGenes Relevant to Other Glycan Degradation		*p*-Value [c]	
	Name	No [b]	Raw	Adjusted [d]
M	NEU3, GBA, MAN2C1, GBA2	4	$\mathbf{3.0 \times 10^{-3}}$	$\mathbf{4.2 \times 10^{-2}}$
P	GBA, MAN2C1, GBA2	3	$\mathbf{4.6 \times 10^{-3}}$	5.0×10^{-2}
AL	MAN2C1	1	1.0×10^{-1}	2.9×10^{-1}
AM	MAN2C1, GBA2	2	$\mathbf{3.3 \times 10^{-2}}$	2.1×10^{-1}
AP	MAN2C1, GBA2	2	$\mathbf{1.6 \times 10^{-2}}$	9.3×10^{-2}
LM	MAN2C1	1	9.0×10^{-2}	2.4×10^{-1}
LP	MAN2C1	1	9.6×10^{-2}	2.7×10^{-1}
MP	GBA, MAN2C1, GBA2	3	$\mathbf{9.4 \times 10^{-4}}$	$\mathbf{7.7 \times 10^{-3}}$
ALM	MAN2C1	1	7.2×10^{-2}	1.5×10^{-1}
ALP	MAN2C1	1	8.1×10^{-2}	2.0×10^{-1}
AMP	MAN2C1, GBA2	2	$\mathbf{1.0 \times 10^{-2}}$	5.1×10^{-2}
LMP	MAN2C1	1	7.6×10^{-2}	1.8×10^{-1}
ALMP	MAN2C1	1	7.2×10^{-2}	1.5×10^{-1}

[a] Two or more letters indicate that enrichment was analyzed using eGenes shared by tissues. A: visceral adipose tissue; L: liver; M: skeletal muscle; P: pancreas. [b] There was a total of 18 other glycan degradation-related genes in the KEGG pathway. [c] Significance with $p < 0.05$ is presented in bold. [d] Adjusted *p*-values were obtained using the Benjamini–Hochberg method to correct for multiple testing.

4. Discussion

4.1. Identification of Pathways with eGenes

This study identified a total of 556 eGenes associated with visceral adipose tissue, 176 eGenes associated with the liver, 715 eGenes associated with skeletal muscle, and 384 eGenes associated with the pancreas, all of which were linked to 2857 independent T2DM GWAS signals. Furthermore, these eGenes were found to be enriched in 12 KEGG pathways for visceral adipose tissue, 18 pathways for the liver, 22 pathways for skeletal muscle, and 20 pathways for the pancreas. Importantly, these pathways were novel findings that were not identified when analyzing the mapped genes physically close to T2DM GWAS signals.

4.2. Lysosomal Pathway

Notably, after excluding MHC-related pathways, which may have spurious significance due to strong linkage, only two significant pathways remained: 'lysosome' for the pancreas and 'other glycan degradation' for skeletal muscle. The 'lysosome' pathway plays a critical role in various cellular processes, including apoptotic cell death, intracellular pathogen killing, antigen presentation, plasma membrane repair, cell adhesion and migration, energy metabolism, tumor invasion and metastasis, metabolic signaling, and gene regulation. Most importantly, lysosomes are responsible for the degradation of cellular waste materials through autophagy and endocytosis. The dysregulation of autophagy in pancreatic beta cells has been extensively studied in the context of T2DM pathogenesis. Studies have shown that Zucker diabetic fatty rats exhibit ubiquitinated protein aggregates in pancreatic beta cells during hyperglycemia [19]. Additionally, knockout mice for the autophagy gene Atg7 showed reduced beta cell numbers, impaired glucose tolerance, and decreased insulin secretion [20]. The present study suggests that the pathogenic mechanism of T2DM may involve a failure of the autophagic termination process associated with lysosomes. This finding aligns with previous studies that have observed the accumulation of autophagosomes in pancreatic beta cells in T2DM, which is associated with impaired insulin secretion and beta cell apoptosis [20–22]. While the activation of the mTOR sig-

naling pathway has received significant attention in the dysregulation of autophagy in T2DM [23,24], other mechanisms underlying the dysregulation of autophagy in T2DM remain unclear. This study highlights the importance of investigating the failure of the autophagic termination process associated with lysosomes as a priority for understanding the pathogenesis of T2DM. Understanding how lysosomal dysfunction contributes to T2DM would lead to better diagnostic tools and strategies for early detection of the disease. Moreover, it is necessary to discover specific genetic factors, proteins, and signaling pathways involved in lysosomal function, which may have significant clinical implications in prevention, diagnosis, and treatment of T2DM in the future.

4.3. eGenes for Lysosomal Pathway

The eGenes shared by skeletal muscle and pancreas exhibited the most significant enrichment in the analysis ($p = 8.4 \times 10^{-5}$). These eGenes encode NPC1, IDUA, HYAL3, GBA, CTSH, AP3S2, ABCB9, and AP3B2. There is suspicion of potential pathogenic mechanisms related to lysosomal dysfunction that link some of these eGenes to T2DM. For instance, NPC1, which is located in the lysosomal membrane, is responsible for transporting low-density lipoproteins from the late lysosomal interior to the cytoplasm. Mutations in this gene, such as rs80358259 (Ile1061Thr), lead to Niemann-Pick type C disease, a neurodegenerative lysosomal disorder characterized by disrupted lipid metabolism and the accumulation of cholesterol and glycosphingolipids in the lysosomes of the brain, lungs, liver, and spleen [25]. Moreover, common exonic variants in NPC1, rs1805082 (Ile858Val) and rs1788799 (Met642Ile), which encode its major structural domains, have shown associations with susceptibility to T2DM as well as obesity ($p < 0.05$) [10]. GBA, another lysosomal membrane protein, cleaves the beta-glucosidic linkage of glycosylceramide. Mutations in this gene can cause Gaucher disease, characterized by the accumulation of glucocerebrosides in lysosomes [26]. CTSH is a cysteine cathepsin that plays a critical role in the degradation of lysosomal proteins. IDUA and HYAL3 are involved in the lysosomal degradation of glycosaminoglycans. However, the functions of AP3S2, ABCB9, and AP3B2 have not been well determined.

5. Conclusions

In conclusion, our findings demonstrate that spatial eGenes associated with T2DM GWAS signals are enriched in the lysosomal pathway. This highlights the autophagic termination process related to lysosomes as a potential pathogenic mechanism underlying T2DM. Some eGenes, including NPC1, IDUA, HYAL3, GBA, and CTSH, which contribute to this enrichment, have the potential to contribute to lysosomal dysfunction-based pathogenic mechanisms in T2DM. Although this study is based on T2DM GWAS signals, the lysosomal pathway was inferred from the eGenes associated with genetic variation in normal individuals. Differential eGene expression between T2DM patients and controls would confirm the target genetic risk factors for T2DM susceptibility suggested in this study. To gain a deeper understanding of the pathology and genetic etiology of T2DM, further experimental studies are required to elucidate the underlying mechanisms that link eGene-based lysosomal dysfunction to susceptibility to T2DM.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/app131810447/s1, Table S1: Significant KEGG terms resulted from the enrichment analysis with eGenes of visceral adipose tissue; Table S2: Significant KEGG terms resulted from the enrichment analysis with eGenes of liver; Table S3: Significant KEGG terms resulted from the enrichment analysis with eGenes of skeletal muscle; Table S4: Significant KEGG terms resulted from the enrichment analysis with eGenes of pancreas; Table S5: Significant KEGG term resulted from the enrichment analysis with mapped genes of T2D GWAS signals.

Author Contributions: Y.K. and C.L. designed the study, interpreted the results, and wrote the manuscript. Y.K. conducted data analyses. C.L. supervised the study. All authors have read and agreed to the published version of the manuscript.

Funding: This research was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF), funded by the Ministry of Education, grant number 2021R1A6A1A10044154.

Institutional Review Board Statement: Ethical review and approval were waived for this study because we used publicly available population-based secondary data and subjects could not be identified.

Informed Consent Statement: Not applicable.

Data Availability Statement: The data used in this study are publicly available in the GTExPortal (dbGaP Accession phs000424.v8.p2).

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Johnson, A.M.; Olefsky, J.M. The Origins and Drivers of Insulin Resistance. *Cell* **2013**, *152*, 673–684. [CrossRef]
2. Ighodaro, O.M. Molecular pathways associated with oxidative stress in diabetes mellitus. *BioMedicine* **2018**, *108*, 656–662. [CrossRef]
3. Sladek, R.; Rocheleau, G.; Rung, J.; Dina, C.; Shen, L.; Serre, D.; Boutin, P.; Vincent, D.; Belisle, A.; Hadjadj, S.; et al. A genome-wide association study identifies novel risk loci for type 2 diabetes. *Nature* **2007**, *445*, 881–885. [CrossRef]
4. Zeggini, E.; Weedon, M.N.; Lindgren, C.M.; Frayling, T.M.; Elliott, K.S.; Lango, H.; Timpson, N.J.; Perry, J.R.B.; Rayner, N.W.; Freathy, R.M.; et al. Replication of Genome-Wide Association Signals in UK Samples Reveals Risk Loci for Type 2 Diabetes. *Science* **2007**, *316*, 1336–1341. [CrossRef]
5. Scott, L.J.; Mohlke, K.L.; Bonnycastle, L.L.; Willer, C.J.; Li, Y.; Duren, W.L.; Erdos, M.R.; Stringham, H.M.; Chines, P.S.; Jackson, A.U.; et al. A Genome-Wide Association Study of Type 2 Diabetes in Finns Detects Multiple Susceptibility Variants. *Science* **2007**, *316*, 1341–1345. [CrossRef]
6. Chimienti, F.; Devergnas, S.; Favier, A.; Seve, M. Identification and cloning of a beta-cell-specific zinc transporter, ZnT-8, localized into insulin secretory granules. *Diabetes* **2004**, *53*, 2330–2337. [CrossRef]
7. Chimienti, F.; Favier, A.; Seve, M. ZnT-8, A Pancreatic Beta-Cell-Specific Zinc Transporter. *BioMetals* **2005**, *18*, 313–317. [CrossRef]
8. Xue, A.; Wu, Y.; Zhu, Z.; Zhang, F.; Kemper, K.E.; Zheng, Z.; Yengo, L.; Lloyd-Jones, L.R.; Sidorenko, J.; Wu, Y.; et al. Genome-wide association analyses identify 143 risk variants and putative regulatory mechanisms for type 2 diabetes. *Nat. Commun.* **2018**, *9*, 2941. [CrossRef]
9. Keildson, S.; Fadista, J.; Ladenvall, C.; Hedman, Å.K.; Elgzyri, T.; Small, K.S.; Grundberg, E.; Nica, A.C.; Glass, D.; Richards, J.B.; et al. Expression of phosphofructokinase in skeletal muscle is influenced by genetic vari-ation and associated with insulin sensitivity. *Diabetes* **2014**, *63*, 1154–1165. [CrossRef]
10. Morris, A.P.; Voight, B.F.; Teslovich, T.M.; Ferreira, T.; Segrè, A.V.; Steinthorsdottir, V.; Strawbridge, R.J.; Khan, H.; Grallert, H.; Mahajan, A.; et al. Large-scale association analysis provides insights into the genetic architecture and pathophysiology of type 2 diabetes. *Nat. Genet.* **2012**, *44*, 981–990. [CrossRef]
11. Azarova, I.; Klyosova, E.; Polonikov, A. The link between type 2 diabetes mellitus and the polymorphisms of glutathi-one-metabolizing genes suggests a new hypothesis explaining disease initiation and progression. *Life* **2021**, *11*, 886. [CrossRef]
12. Marselli, L.; Piron, A.; Suleiman, M.; Colli, M.L.; Yi, X.; Khamis, A.; Carrat, G.R.; Rutter, G.A.; Bugliani, M.; Giusti, L.; et al. Persistent or transient human β cell dysfunction induced by metabolic stress: Specific signatures and shared gene expression with type 2 diabetes. *Cell Rep.* **2020**, *33*, 108466. [CrossRef]
13. Maude, H.; Lau, W.; Maniatis, N.; Andrew, T. New Insights into Mitochondrial Dysfunction at Disease Susceptibility Loci in the Development of Type 2 Diabetes. *Front. Endocrinol.* **2021**, *12*, 694893. [CrossRef]
14. Kusminski, C.M.; Bickel, P.E.; Scherer, P.E. Targeting adipose tissue in the treatment of obesity-associated diabetes. *Nat. Rev. Drug Discov.* **2016**, *15*, 639–660. [CrossRef]
15. Hindorff, L.A.; Sethupathy, P.; Junkins, H.A.; Ramos, E.M.; Mehta, J.P.; Collins, F.S.; Manolio, T.A. Potential etiologic and functional implications of genome-wide association loci for human diseases and traits. *Proc. Natl. Acad. Sci. USA* **2009**, *106*, 9362–9367. [CrossRef]
16. Aguet, F.; Barbeira, A.N.; Bonazzola, R.; Jo, B.; Kasela, S.; Liang, Y.; Parsana, P.; Aguet, F.; Battle, A.; Brown, A.; et al. The GTEx Consortium The GTEx Consortium atlas of genetic regulatory effects across human tissues. *Science* **2020**, *369*, 1318–1330. [CrossRef]
17. Ongen, H.; Buil, A.; Brown, A.A.; Dermitzakis, E.T.; Delaneau, O. Fast and efficient QTL mapper for thousands of molecular phenotypes. *Bioinformatics* **2015**, *32*, 1479–1485. [CrossRef]
18. Xie, Z.; Bailey, A.; Kuleshov, M.V.; Clarke, D.J.B.; Evangelista, J.E.; Jenkins, S.L.; Lachmann, A.; Wojciechowicz, M.L.; Kropiwnicki, E.; Jagodnik, K.M.; et al. Gene Set Knowledge Discovery with Enrichr. *Curr. Protoc.* **2021**, *1*, e90. [CrossRef]
19. Kaniuk, N.A.; Kiraly, M.; Bates, H.; Vranic, M.; Volchuk, A.; Brumell, J.H. Ubiquitinated-protein aggregates form in pancreatic beta-cells during diabetes-induced oxidative stress and are regulated by autophagy. *Diabetes* **2007**, *56*, 930–939. [CrossRef]

20. Kim, J.; Cheon, H.; Jeong, Y.T.; Quan, W.; Kim, K.H.; Cho, J.M.; Lim, Y.-M.; Oh, S.H.; Jin, S.-M.; Kim, J.H.; et al. Amyloidogenic peptide oligomer accumulation in autophagy-deficient β cells induces diabetes. *J. Clin. Investig.* **2014**, *124*, 3311–3324. [CrossRef]
21. Ebato, C.; Uchida, T.; Arakawa, M.; Komatsu, M.; Ueno, T.; Komiya, K.; Azuma, K.; Hirose, T.; Tanaka, K.; Kominami, E.; et al. Autophagy Is Important in Islet Homeostasis and Compensatory Increase of Beta Cell Mass in Response to High-Fat Diet. *Cell Metab.* **2008**, *8*, 325–332. [CrossRef]
22. Masini, M.; Bugliani, M.; Lupi, R.; del Guerra, S.; Boggi, U.; Filipponi, F.; Marselli, L.; Masiello, P.; Marchetti, P. Autophagy in human type 2 diabetes pancreatic beta cells. *Diabetologia* **2009**, *52*, 1083–1086. [CrossRef]
23. Bartolomé, A.; Kimura-Koyanagi, M.; Asahara, S.I.; Guillén, C.; Inoue, H.; Teruyama, K.; Shimizu, S.; Kanno, A.; García-Aguilar, A.; Koike, M.; et al. Pancreatic β-cell failure mediated by mTORC1 hyperactivity and au-tophagic impairment. *Diabetes* **2014**, *63*, 2996–3008. [CrossRef]
24. Blandino-Rosano, M.; Barbaresso, R.; Jimenez-Palomares, M.; Bozadjieva, N.; Werneck-De-Castro, J.P.; Hatanaka, M.; Mirmira, R.G.; Sonenberg, N.; Liu, M.; Rüegg, M.A.; et al. Loss of mTORC1 signalling impairs β-cell homeostasis and insulin processing. *Nat. Commun.* **2017**, *8*, 16014. [CrossRef]
25. Lamri, A.; Pigeyre, M.; Garver, W.S.; Meyre, D. The Extending Spectrum of NPC1-Related Human Disorders: From Niemann–Pick C1 Disease to Obesity. *Endocr. Rev.* **2018**, *39*, 192–220. [CrossRef]
26. Hruska, K.S.; LaMarca, M.E.; Scott, C.R.; Sidransky, E. Gaucher disease: Mutation and polymorphism spectrum in the glucocerebrosidase gene (GBA). *Hum. Mutat.* **2008**, *29*, 567–583. [CrossRef]

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.