Supplementary data 11. Tissue-specific gene expression correlated with T2D-associated alleles of *GSS* and *GGT7* genes and disease pathogenesis

The figure depicts the puzzle showing genes whose tissue-specific changes in expression level were correlated with a carriage of the T2D-associated polymorphisms of *GSS* and *GGT7* genes, and associated with the risk of type 2 diabetes. Understanding a source of these complex interrelationships will bring us to deciphering the molecular mechanisms by which the *GSS* and *GGT7* genes and other genes for glutathione metabolism are involved in the pathophysiology of type 2 diabetes.

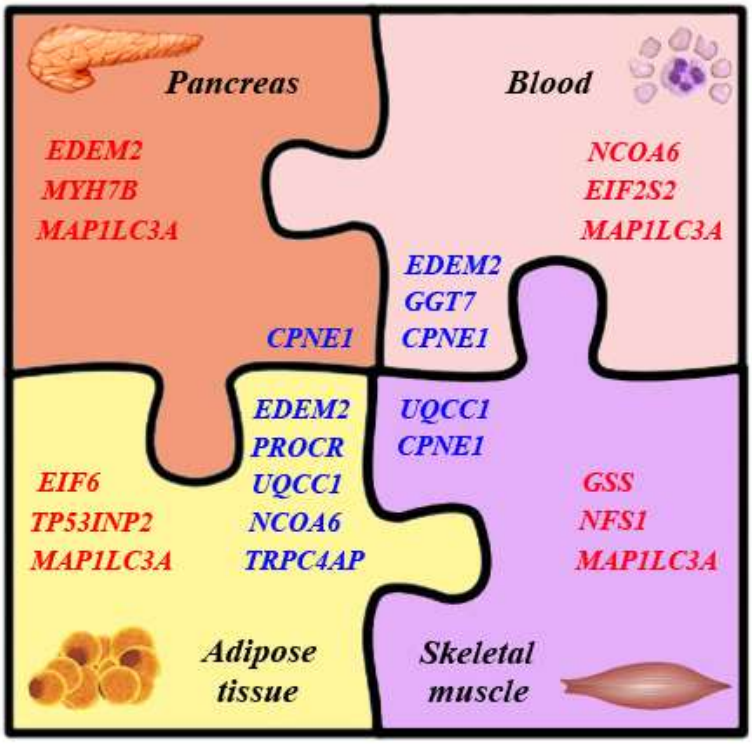

Figure. Tissue-specific changes in the expression level of genes that associated with the disease related polymorphisms of *GSS* and *GGT7* genes, as *in silico* predicted by the TWAS analysis in type diabetes

Blue and red colors depict genes whose tissue expression in diabetics is decreased and increased, respectively. EDEM2, endoplasmic reticulum degradation-enhancing alpha-mannosidase-like protein 2; MYH7B, myosin heavy chain 7B; PROCR, endothelial protein C receptor; MAP1LC3A, microtubule-associated proteins 1A/1B light chain 3A; TRPC4AP, short transient receptor potential channel 4-associated protein; TP53INP2, tumor protein p53-inducible nuclear protein 2; NFS1, mitochondrial cysteine desulfurase; EIF2S2, eukaryotic translation initiation factor 2 subunit beta; EIF6, eukaryotic translation initiation factor 6; CPNE1, cAMP responsive element binding protein 1; UQCC1, ubiquinol-cytochrome-c reductase complex assembly factor 1; GGT7, gamma-glutamyltransferase 7; GSS, glutathione synthetase.

Pursuing this interest, we carried out an in-depth analysis of the literature on the biological functions of genes whose expression is interrelated with polymorphic variants of the *GSS* and *GGT7* genes associated with the development of type 2 diabetes. A primary goal was to analyze biological functions of four genes such as *EDEM2*, *MYH7B*, *MAP1LC3A*, and *CPNE1* whose expression level in the pancreas was associated with a carriage of T2D-associated alleles of *GSS* and *GGT7*. Our interest in the pancreas is due to the fact that beta-cells located in this organ produce insulin, a hormone whose impaired maturation and secretion is linked to the development of type 2 diabetes mellitus.

EDEM2 is endoplasmic reticulum (ER) degradation-enhancing alpha-mannosidase-like protein 2, a protein involved in the ER-associated degradation (ERAD) pathway targeting misfolded glycoproteins for degradation in an N-glycan-dependent manner [64]. Endoplasmic reticulum is a multifunctional organelle that represents the Ca2 + reservoir in the cell, the site of protein assembly and folding, the site of steroid synthesis, as well as the platform of intercellular and interorganellar signaling [65]. To restore the accuracy of protein folding, the cell triggers unfolded protein response (UPR), a network of signaling pathways for reprogramming gene transcription, mRNA translation

and post-translational protein modification to restore protein homeostasis also called as proteostasis [65]. Endoplasmic reticulum stress (ER-stress) and associated UPR have been implicated in the pathogenesis of type 2 diabetes as a potential contributor to pancreatic beta-cell dysfunction and linked to diabetes-related phenotypes such as insulin resistance and obesity [66]. It is important to note the loss of activity of UPR participants such as IRE1α, XBP1, ATF6, PERK, and ATF4 is associated with both dysfunction and death of pancreatic beta-cells [67]. As a part of unfolded protein response induced by ER-stress, misfolded and unassembled proteins of the endoplasmic reticulum are subjected to recognition and elimination by the ERAD system, an evolutionarily conserved protein quality control system that destroys the targeted proteins by the cytoplasmic ubiquitin-proteasome pathway [68]. It is important to note that the ERAD system plays a critical role in supporting glucose-stimulated insulin secretion in pancreatic β-cells, and ERAD deficiency may be responsible for the development of diabetes through the impairment of glucose-stimulated insulin secretion that is due to affecting both folding-competent and folding-deficient processing of proteins in the ER [69]. Interestingly, loss-of-function mutations in the *EDEM2* gene are responsible for early-onset childhood diabetes [70]. Experimental down-regulation of *Edem2* in rat β-cells has been found to reduce the expression of genes involved in the glucose-stimulated insulin secretion pathway such as *Glut2* and *Pxd1*, ultimately leading to suppression of insulin secretion, but not apoptosis [70]. The TWAS analysis enabled us identifying that the expression level of *EDEM2* was increased in the pancreas in diabetics, pointing out that *EDEM2* is potentially involved in the ER-associated degradation of proteins in pancreatic tissue, in particular, it may target misfolded and unfolded proinsulin for proteasomal degradation. We hypothesize that the increased expression of *EDEM2* in the pancreas in patients with T2D may be considered as a sign of adaptive activation of the ER-associated protein degradation as a part of unfolded protein response, the hallmark in type 2 diabetes pathogenesis.

Pancreatic changes in the expression of *MYH7B*, a structural part of myosin in non-muscle cells, pays a special attention since the protein may be involved the transmembrane transport of glucose. MYH7B, myosin heavy chain 7B is a structural part of myosin, the major contractile protein mostly expressed in cardiomyocytes and skeletal muscle cells. It is well known that skeletal muscle is the major site for insulin-stimulated glucose disposal, and skeletal muscle insulin resistance is the key pathological condition in type 2 diabetes [71]. Alterations in the expression of myosin heavy chains in skeletal muscle can be induced by a variety of factors including physical activity, obesity, aging, and high fat/high sugar diet, i.e. the factors playing an essential role in the development of type 2 diabetes [72]. It has been revealed that myosin heavy chain isoforms impact insulin-stimulated glucose uptake by skeletal muscle cells in rats [73]. Interestingly, MYH7B is also found in non-muscle cells, but nothing is known about its functional roles in such types of cells including beta-cells of the pancreatic islets. A study in humans showed that the non-muscle myosin *MYH9* (myosin heavy chain 9, a marker of fast-twitch oxidative fiber and an analog of MYH7B) gene expression related positively with insulin-stimulated glucose uptake, whereas the expression levels of muscle myosin *MYH1* (myosin heavy chain 1, a marker fast-twitch glycolytic fiber) related negatively with insulin-stimulated glucose uptake [74]. Other studies have established that non-muscle myosins may play a role in the GLUT4 (insulin-responsive glucose transporter type 4) vesicle trafficking required for insulin-stimulated glucose uptake [75]. Interestingly, Liu with co-authors have recently observed an increased expression of *Myh7b* among 10 differentially expressed genes in the liver of rats with experimental type 2 diabetes [20]. A 5-week therapy of T2D rats with walnut meal extracts (walnut is rich in polyphenols and glutathione) resulted in decreasing of *Myh7b* expression that accompanied by a) decreasing fasting blood glucose and insulin resistance, b) increasing β-cell function and insulin sensitivity index, c) improving body weight, oral glucose tolerance test and insulin sensitivity, d) increasing the activities of antioxidant enzymes, and e) decreasing the levels of malondialdehyde in the liver and serum [76]. These experimental findings clearly show that the restoration of glutathione content in diabetics has the potential of decreasing fasting blood glucose, improving insulin sensitivity, and reducing oxidative stress. The TWAS analysis allowed us to observe the association between the increased levels of *MYH7B* in pancreatic tissue and with type 2 diabetes, supporting the findings of Li with co-authors [186] that there is a causal relationship between the increased level of *MYH7B* and susceptibility to type 2 disease. It can be assumed that the increased tissue level of *MYH7B* in diabetics may indicate increased insulin-stimulated glucose uptake by the cell that may be due to intracellular deficiency of glutathione. Although it is obvious that this protein is important for the disease development, at least due to its participation in the regulation of insulin-stimulated glucose uptake by the cell, a limited information on functions of this form of myosin in non-muscle cells does not now allow to draw a definitive conclusion on the roles of *MYH7B* in the pathogenesis of type 2 diabetes.

Autophagy is a post-endoplasmic reticulum pathway necessary for effective turnover of misfolded or aggregated proteins, clearing damaged organelles as well as for cellular survival under various stress stimuli [77]. In the pancreatic b-cells, autophagy is important for regulating proinsulin levels and insulin secretion, and the autophagic

degradation of proinsulin may have pathophysiological implications for the development of insulin deficiency in type 2 diabetes [78]. MAP1LC3A, microtubule-associated proteins 1A/1B light chain 3A is ubiquitin-like modifier protein mediating the physical interactions between microtubules and components of the cytoskeleton and involved in the formation of autophagosomes [79]. Upon nutrient stress, MAP1LC3A together with the reticulophagy receptor TEX264 plays a role in the remodeling of subdomains of the endoplasmic reticulum into autophagosomes [80], thereby playing a role in the regulation of autophagy. Autophagy is a post-endoplasmic reticulum pathway necessary for effective turnover of misfolded or aggregated proteins, clearing damaged organelles as well as for cellular survival under various stress stimuli [81]. In the pancreatic b-cells, autophagy is important for regulating proinsulin levels and insulin secretion, and the autophagic degradation of proinsulin may have pathophysiological implications for the development of insulin deficiency in type 2 diabetes [82]. Urinary expression of MAP1LC3A is considered as autophagy markers in patients with diabetic kidney disease [83]. Notably, the TWAS analysis allowed us identifying that the increased expression of *MAP1LC3A* in the pancreas, skeletal muscle, adipose tissue, and whole blood is associated with the susceptibility to type 2 diabetes. An increased multi-tissue expression level of *MAP1LC3A*, an ubiquitin-like modifier protein involved in the formation of autophagosomes [89], may indicate the systemic activation of autophagy, a post-endoplasmic reticulum pathway focused on effective turnover of misfolded or aggregated proteins [82]. In the pancreatic beta-cells, increased MAP1LC3A may have a protective role against ER-stress-mediated cell death through the autophagic degradation of misfolded or unfolded proinsulin molecules that have been established in type 2 diabetes [84,85,86]. It can be assumed that an increase in *MAP1LC3A* expression in the pancreas, skeletal muscle, and adipose tissue in diabetics depicts the increased autophagosome activation as a process of physiologic response of pancreas and insulin-sensitive tissues to the ER-induced stress and unfolded protein response attributed to the accumulation of unfolded/misfolded proteins in the ER lumen. A crosstalk between unfolded protein response and autophagy is known form the literature: the UPR may induce autophagy and vice versa autophagy can alleviate the UPR.

CPNE1, cAMP responsive element binding protein 1, is a calcium-dependent phospholipid-binding protein regulating a variety of intracellular molecular processes at the interface of the cell membrane and cytoplasm such as membrane trafficking, recruiting target proteins to the cell membrane [87,88,89]. CPNE1 is involved in TNF-alpha-induced transcriptional repression of NF-kappa-B by inducing endoprotease processing of transcription factor-protein complexes including NF-kappa-B p65/NFKB1, NF-kappa-B p50/NFKB1, p52/NFKB2, RELB and REL [90,91]. Interestingly, the increased levels of *Cpne1* were found in the β-cells of the pancreas of the streptozotocin-diabetic rats, a model of the chronic complications of human type 2 diabetes [202]. Since CPNE1 has the potential to control the transcription of NF-kappa-B, involved in cellular responses to various stress stimuli such as cytokines, free radicals, heavy metals, etc, and transcriptional repression of NF-kappa-B by CPNE1 could impact the inflammatory response and cell survival through susceptibility of the cell to apoptosis [93], a key pathophysiological process underlying β-cell damage in type 2 diabetes [94]. Notably, the TWAS analysis has shown that decreased levels of *CPNE1* in the pancreas, skeletal muscle, and whole blood were associated with the risk of type 2 diabetes. Based on existing biological functions of CPNE1, its decreased level, on the one hand, may be indicative for the inflammatory state of these tissues and their increased susceptibility to apoptosis, on the other hand, the decreased *CPNE1* may impair insulin secretion through the cell membrane. In addition, since CPNE1 exhibits a repressive effect on transcription factor NF-kappa-B, the decreased levels of CPNE1 in diabetics may facilitate an excessive activation of NF-κB signaling leading to induction of pro-inflammatory genes, including cytokines and chemokines that play a role in the pathogenesis of type 2 diabetes [95].

As can be seen from Figure, several other genes whose expression levels in insulin-sensitive tissues such as skeletal muscle, adipose tissue and also in whole blood were found to be correlated with both the genetic risk of type 2 diabetes and a carriage of disease-associated alleles of *GSS* and *GGT7* genes.

The *TP53INP2* (tumor protein p53-inducible nuclear protein 2) gene encodes a bifunctional protein acting as a transcriptional coactivator and as a key regulator of basal autophagy by stimulation of autophagosome formation and ubiquitinated protein degradation [96,97]. We found that *TP53INP2* expression in whole blood is negatively correlated with a carriage of T2D-associated allele rs11546155-A of the *GGT7* gene, thereby suggesting the link between glutathione metabolism with both autophagy and protein degradation.

The decreased expression of TRPC4AP in adipose tissue and liver were correlated with a carriage of T2D-associated allele rs13041792-A of the *GSS* gene. TRPC4AP (short transient receptor potential channel 4-associated protein) is a membrane protein involved in the transport of extracellular Ca2+ to cytosol and elevation of endoplasmic reticulum Ca^{2+} storage reduction in response to muscarinic acetylcholine receptor-1 [98]. TRPC4AP was enriched with the PathCards pathway "Transport of glucose and other sugars, bile salts and organic acids, metal ions and amine

compounds" (https://www.genecards.org) suggesting that the protein may participate in the transport of glucose across the cell membrane. The involvement of TRPC4AP in glucose transport can be supported by the findings of Malenczyk with coworkers who established the increased expression of *TRPC4AP* in β-cells from patients with T2D diabetics [99]. TRPC4AP acts as a substrate-specific adapter for a DCX E3 ubiquitin-protein ligase complex which participates in the control of cell cycle and specifically mediates the polyubiquitination and subsequent degradation of MYC [98], a transcription factor that is known to upregulate glucose and glutamine transporters as well as key enzymes in the glycolytic or glutaminolysis pathways [100]. In addition, TRPC4AP plays an essential role in regulating inflammation via the meditation of NF-κB signaling in inflammation [98,101], and *trpc4ap*-knockout mice exhibit decreased serum glucose and insulin levels along with decreased expression of pro-inflammatory cytokines which accompanied by the inactivation of the IKKα/IκBα/NF-κB pathway [101,102].

The TWAS bioinformatics analysis allowed us identifying the decreased expression of *NCOA6* in adipose tissue and increased expression of *NCOA6* in blood was associated with the genetic risk of type 2 diabetes. NCOA6 is a nuclear receptor coactivator 6 with a range of pleiotropic effects on various biological functions including growth, development, wound healing, and maintenance of energy homeostasis [103]. Experimental studies provided some evidence that NCOA6 could be a biomarker of human type 2 diabetes, and the involvement of NCOA6 in T2D pathogenesis might be related to the regulation of insulin secretion in the cellular response to a glucose stimulus [104]. A study conducted by Yeom and colleagues [105] showed that the overexpression of *Ncoa6* increased glucose-elicited insulin secretion, whereas *Ncoa6*-knockout mice exhibited the decreased insulin secretion in pancreatic islets. Moreover, *Ncoa6*-knockout mice showed reduced islet mass and number, which correlated with increased apoptosis and decreased proliferation of their pancreatic islets. Taking together, these findings point out that NCOA6 is an important regulator of insulin secretion and β-cell mass maintenance, and the reduced expression or activity of NCOA6 may linked with abnormal insulin secretion, a characteristic feature of type 2 diabetes. Additionally, NCOA6 is a co-activator of NF-kappa-B pathway [106], therefore the increased blood levels of *NCOA6* may be responsible for stimulating cellular signaling pathways linking to inflammation that play a role in type 2 diabetes.

We found that the increased levels of *NFS1* in skeletal muscle are related to genetic susceptibility to type 2 diabetes and was found to be positively correlated to a carriage of T2D-associated allele (rs13041792-A) at glutathione synthetase gene. NFS1 (cysteine desulfurase) is a mitochondrial enzyme that belongs to the family sulfurtransferases involved in the transfer of sulfur-containing groups. As a part of the sulfur relay system, NFS1 supplies inorganic sulfur to the Fe-S clusters required for the function of cellular enzymes by removing the sulfur from cysteine and other sulfur-containing amino acids [107,108] as well as known to play essential roles in energy metabolism, transcriptional regulation, DNA repair, and biosynthesis of nucleotides and amino acids [109]. Importantly, the maturation of Fe-S proteins requires glutathione [110]. Interestingly, the expression levels of NFS1 are significantly repressed in skeletal muscle from *Ndufab1*-knockout mice and accompanied by disruption of glucose homeostasis [111]. NDUFAB1 is an NADH: ubiquinone oxidoreductase subunit AB1, also known as mitochondrial acyl carrier protein transferring electrons from NADH to the respiratory chain [112] and acting as an enhancer of mitochondrial metabolism, protecting against obesity and insulin resistance [111]. Thus, the increased expression of *NFS1* may reflect, on the one hand, activation of the sulfur relay system, on the other hand, enhanced mitochondrial metabolism. It is known that mitochondrial function represents an integral part of glucose-stimulated insulin secretion in pancreatic β-cells and plays a key role in skeletal muscle oxidative phosphorylation [113]. It is well known that a pronounced increase in mitochondrial respiration is required for the synthesis and release of insulin by pancreatic β-cells adequately to uptake and metabolism of nutrients. Mitochondrial dysfunction as an important part of the pathogenesis of insulin resistance and T2D is manifested by high production of reactive oxygen species and low levels of ATP and thought to be related to changes in the autophagic process, endoplasmic reticulum stress, and inflammation [114]. Thus, based on literature data of biological functions of NFS1, we suggest that the increased expression of *NFS1* in insulin-resistant skeletal muscle cells occurring in diabetics, on the one hand, may be considered as a marker of adaptive enhance of mitochondrial functions for efficient energy production in the skeletal muscle requires oxidative phosphorylation [115, 116], on the other hand, the increased expression of *NFS1* in skeletal muscle in diabetics may mirror a demand of mitochondria in the active Fe-S proteins required for energy metabolism [109], and the lack of active Fe-S proteins is known to be exacerbated by a deficiency of intracellular glutathione [110].

The TWAS analysis showed that decreased levels of *UQCC1* in insulin-sensitive tissues such as skeletal muscle and adipose tissues are strongly associated with a diagnosis of type 2 diabetes in two cohorts from the UK Biobank (Figure 3). Moreover, the present study showed that two polymorphisms such as rs13041792 of *GSS* and rs6119534 of *GGT7* are associated with both the risk of type 2 diabetes and decreased levels of *UQCC1* in whole blood. This finding may suggest a relationship between glutathione metabolism and mitochondrial enzymes participating in cell

respiration and ATP production. UQCC1, ubiquinol-cytochrome-c reductase complex assembly factor 1 is a protein required for the assembly of the ubiquinol-cytochrome c reductase complex (complex III) is an energy-transducing, electron-transfer enzyme located in the inner mitochondrial membrane and participated in cell respiration [117]. This mitochondrial complex oxidizes quinol and reduces a water-soluble, c-type cytochrome linking this redox reaction to translocation of protons across the membrane, thereby contributing to the generation of proton motive force used for ATP synthesis [118]. UQCC1 promotes complex III synthesis and stability, thereby participating in cytochrome *b* biogenesis [117,119]. Taking into account the above functions of UQCC1, the decreased level of *UQCC1* in adipose tissue and skeletal muscle might be responsible for UQCC1-dependent perturbation in cytochrome *b* expression and subsequent decreasing the efficiency of cellular energy conversion, increasing ROS production, ultimately leading to oxidative stress, mitochondrial dysfunction - characteristic metabolic abnormalities underlying type 2 diabetes [120]. We also found that the increased levels of *EIF6* in adipose tissue were correlated to the risk of type 2 diabetes. EIF6 is eukaryotic translation initiation factor 6 also known as integrin beta 4 binding protein. EIF6 acts as a stimulatory factor for the initiation of translation of downstream insulin or growth factors, and cells with the decreased amount of EIF6 do not increase translation in response to insulin [121,122]. Moreover, EIF6 has been shown to control fatty acid synthesis and glycolysis in liver and fat tissue, where EIF6 acts by exerting translational control of adipogenic transcription factors such as CEBPB, CEBPD, and ATF4, thereby reshaping gene expression with increased levels of lipogenic and glycolytic enzymes [123]. It is important to add that EIF6 controls the transcriptional activity of genes encoding mitochondrial respiratory chain producing reactive oxygen species [124], and it has been revealed a correlation between expression of EIF6 and the levels of C-reactive protein, a marker of systemic inflammation [125]. We propose that the increased levels of *EIF6* in adipose tissue of patients with type 2 diabetes appear to enhance the production of adipogenic transcription factors activating the expression of genes for lipogenic and glycolytic enzymes necessary for energy production. The TWAS bioinformatics analysis revealed that a sharp increase in blood levels of *EIF2S2* is genetically linked to type 2 diabetes (Figure 3) and also associated with a carriage of rs13041792-A of GSS that has been also associated with the disease risk. EIF2S2 (eukaryotic translation initiation factor 2 subunit beta) is a member of eukaryotic translation initiation factors (eIF2) that functions in the early steps of protein synthesis through the formation of the ternary complex with GTP and initiator tRNA and binding to the 40S subunit of ribosomes [126]. Like eIF2, phosphorylation-dephosphorylation reactions of EIF2S2 contribute to glucose-induced activation of protein biosynthesis [127]. The eIF2α kinase PERK (RNA-dependent protein kinase-like ER kinase) is the key mediator of the translation arm of the unfolded protein response by rapidly decreasing the protein load on the endoplasmic reticulum via translational repression of mRNAs encoding secreted proteins [128]. Palam with colleagues suggested that high eIF2 levels are required for efficient translation of the target genes during ER stress-induced unfolded protein response [129]. Thus, based on biological functions of EIF2S2, the increased expression of this gene in blood of diabetes may be interpreted as a sign of the repressed protein synthesis machinery attributed to the endoplasmic reticulum ER stress and activation of unfolded protein response. The TWAS analysis has shown that increased level of *EIF2S2* along with decreased level of *GGT7* in blood are linked with genetic risk of type 2 diabetes. We suggest that the decreased level of *GGT7* in blood in diabetics mirrors a deficiency of this enzyme that may cause a decreased rate of glutathione utilization by peripheral tissues since gamma-glutamyl transferase is involved in glutathione recycling, supplementing the cell with GSH precursors. Thus, tissue-specific changes in gene expression that correlated with T2D-associated alleles of *GSS* and *GGT7* genes may mirror various pathological disorders established in type 2 diabetes mellitus.

Supplementary references

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