Aspects of Molecular Medicine 4 (2024) 100046

Contents lists available at ScienceDirect

Aspects of Molecular Medicine

journal homepage: www.journals.elsevier.com/aspects-of-molecular-medicine

Genome-wide linkage and association of novel genes and pathways with type 2 diabetes in Italian families

Mutaz Amin [a,b], Claudia Gragnoli [c,d,e,f,*]

[a] INSERM, US14-Orphanet, Paris, 75014, France
[b] Department of Biochemistry and Molecular Biology, Faculty of Medicine, Al-Neelain University, Khartoum, 11121, Sudan
[c] Division of Endocrinology, Department of Medicine, Creighton University School of Medicine, Omaha, NE, 68124, USA
[d] Department of Public Health Sciences, Penn State College of Medicine, Hershey, PA, 17033, USA
[e] Molecular Biology Laboratory, Bios Biotech Multi-Diagnostic Health Center, Rome, 00197, Italy
[f] Klinik für Endokrinologie, Diabetologie und Klinische Ernährung, Universitätsspital Zürich, Zürich, 8091, Switzerland

ARTICLE INFO

Keywords:
Type 2 diabetes
T2D
Single nucleotide polymorphisms
SNPs
Genome-wide
Linkage
Linkage disequilibrium
Genetics
Genomics
Association
Metabolic syndrome
Insulin resistance
Polycystic ovary syndrome
Hyperglycemia
Obesity
Families
Familial
Italy
Italian

ABSTRACT

Background: Type 2 diabetes mellitus (T2D) stands as one of the most prevalent chronic diseases globally, posing substantial health and economic burdens on society. Within the spectrum of T2D, familial cases emerge as a distinct entity characterized by a strong familial clustering of the disease. This phenomenon has long suggested that genetics contributes substantially to T2D susceptibility, motivating extensive research into the genetic determinants of familial T2D.

Methods: We recruited 212 multigenerational Italian families with multiple cases of T2D. The families were genotyped using genomic array ($\geq$ 600k) derived from the UK Biobank Axiom Array platform. Informative markers were tested via Pseudomarker for linkage to and linkage disequilibrium (i.e., linkage joint to association) with T2D across the following models: dominant with complete penetrance (D1), dominant with incomplete penetrance (D2), recessive with complete penetrance (R1), and recessive with incomplete penetrance (R2).

Results: We identified a total of 566 variants reaching genome-wide significant ($P < 0.00005$) linkage and/or association to/with the risk of T2D in Italian families. Of the 355 genes identified in our study, 341 (96%) are novel and have not been reported with T2D or any of its related phenotypes (i.e., obesity, metabolic syndrome, insulin resistance, polycystic ovary syndrome, and hyperglycemia).

Conclusion: Our study constitutes the first familial T2D-linkage and association study in the Italian population. However, the functional relevance of the novel variants and genes reported in our study remains to be explored.

1. Introduction

Type 2 diabetes mellitus (T2D) stands as one of the most prevalent chronic diseases globally, posing substantial health and economic burdens on society (Khan et al., 2020). Although environmental factors such as diet and physical activity play a significant role in T2D development (Dendup et al., 2018), mounting evidence underscores the critical influence of genetics (Ali, 2013). Within the spectrum of T2D, familial cases emerge as a distinct entity characterized by a strong familial clustering of the disease (Hemminki et al., 2010; Murea et al., 2012). This phenomenon has long suggested that genetics contributes substantially to T2D susceptibility (Laakso et al., 2022), motivating extensive research into the genetic determinants of familial T2D.

Numerous genetic studies, particularly genome-wide association studies (GWAS), have uncovered a plethora of susceptibility loci associated with T2D risk (Mahajan et al., 2018; Xue et al., 2018; Meigs, 2019; Kwak et al., 2016; Shojima et al., 2023). These findings have emphasized the polygenic nature of the disease, implicating common genetic variants in its pathogenesis (Shojima et al., 2023). However, familial T2D presents a unique challenge, as it is marked by a heightened genetic predisposition that transcends the typical heritability seen in sporadic cases (Prasad et al., 2015). Families affected by T2D often exhibit a multigenerational history of the disease, suggesting the presence of rare and highly penetrant genetic variants that contribute

* Corresponding author. 6901 N. 72nd St., Creighton University School of Medicine, Omaha, NE, 68122, USA. Tel: (508) 246-9330.
E-mail addresses: mtz88@hotmail.co.uk (M. Amin), claudia.gragnoli@gmail.com (C. Gragnoli).

https://doi.org/10.1016/j.amolm.2024.100046
Received 28 January 2024; Received in revised form 17 May 2024; Accepted 2 June 2024
Available online 4 June 2024

significantly to disease risk (Grarup et al., 2014).

The study of familial T2D genetics seeks to identify the specific genetic variants, pathways, and mechanisms that distinguish these high-risk families from the general population (DeForest et al., 2022). Such insights could not only illuminate the etiological basis of T2D but also enable the identification of at-risk individuals within families, facilitating early intervention and personalized clinical management (Chung et al., 2020) of both T2D and its complications (Nyenwe et al., 2011).

In this study, we embark on a comprehensive exploration of the genetics of familial T2D by conducting the first familial genome-wide linkage and association study of T2D in Italian families, and we report several novel risk variants and genes associated with the risk of T2D.

2. Materials and methods

Two hundred and twelve multigenerational Italian families with multiple cases of T2D were recruited for the study. The families have three generational ascendants from the Italian peninsula. T2D was diagnosed according to the National Diabetes Data Group Criteria: "Presence of hyperglycemia plus the classical signs and/or symptoms of diabetes, or by elevated fasting plasma glucose $\geq$ 140 mg/dl" (Classification and diagnosis of diabetes, 1979). Additionally, for affected individuals, the updated American Diabetes Association criteria were applied, requiring either two instances of fasting glycemia at or above 126 mg/dL, or random glycemia reaching 200 mg/dL with accompanying symptoms, or levels of at least 200 mg/dL 2 h post an oral glucose tolerance test using 75 mg of glucose. Secondary causes of diabetes were systematically excluded, such as pancreatectomy or cystic fibrosis. T2D had to be present in more than one first-degree family member. The mean age at diagnosis stood at 47.85 years (ranging from 7 to 81, with a median of 41). The ratio of males to females was 1.04:1, with an average family size of 5.45. The families were genotyped using genomic array ($\geq$ 600k) derived from the UK Biobank Axiom Array platform. Tested variants were filtered for quality control (QC $\geq$ 0.96) and kinship correlation. All Mendelian and genotyping errors were excluded using PLINK tool (Purcell et al., 2007). The informative markers were tested via Pseudomarker (Hiekkalinna et al., 2011) for linkage to and linkage disequilibrium (i.e., linkage joint to association) with T2D across the following models: dominant with complete penetrance (D1), dominant with incomplete penetrance (D2), recessive with complete penetrance (R1), and recessive with incomplete penetrance (R2). Since there is no prior knowledge of whether the risk variants will be monoallelic or biallelic, we performed the statistical analysis for all inheritance models. Pseudomarker proves to be a robust tool, as it effectively examines both linkage and linkage disequilibrium (LD) within datasets comprising families of diverse structures, doing so with statistical and computational efficiency. Pseudomarker estimates marker allele frequencies, linkage disequilibrium (LD; referring to marker allele frequencies dependent on the putative disease-locus allele), and recombination fractions. It also incorporates LD through "conditional allele frequencies," a methodology that diverges from conventional approaches, as it enables the specification of marker allele frequencies contingent upon the putative disease-locus allele instead of explicitly defining haplotype frequencies (Hiekkalinna et al., 2011). P-values of < 0.00005 were considered statistically significant at genome-wide level. We compared the four models for maximum logarithm of the odds score (LOD) score achieved, to test which one was more informative.

All participants consented to participate in the study which was approved by the Bios Ethical Committee.

2.1. In-silico analysis

Per our initial assessment, we analyzed the significantly detected risk variants using SNP Function Prediction (Xu et al., 2009), SNP2TF (Kumar et al., 2017), and SNPnexus (Chelala et al., 2009) to predict their potential impact on transcription factor binding, splicing, miRNA binding, as well as protein pathogenicity. We used Reactome (Gillespie et al., 2022) to analyze the genes-sets for related pathways and also cross-mapped the positions of the detected risk variants with pancreatic islet enhancer clusters particularly enriched in T2D (Pasquali et al., 2014).

3. Results

We identified a total of 566 variants genome-wide significantly linked and/or associated to/with the risk of T2D in Italian families ($P < 0.00005$) (Figs. 1–4). 362 (64%) variants are within 355 genes (39 variants are within two genes) and 204 (36%) are intergenic. Sixty-nine test statistics from 38 variants have $P < 1.5E\text{-}45$ which is the lowest P reportable by Pseudomarker as zero. The number of genome-wide significant variants under D1, D2, R1 and R2 are 247, 152, 235, and 171, respectively (Fig. 5). The number of variants significant under only one model and multiple models are reported in the Venn diagram (Fig. 5). The majority of intragenic variants are intronic (74%) followed by missense (12%) (Supplementary Table 1). Five variants were in 3′-UTR, and 4 and 7 variants were downstream and 7 upstream, respectively. Splicing and nonsense variants were rare (3 variants each), and 8 variants were synonymous (Supplementary Table 1). The reference allele was the risk allele in half (283) of the variants (50%) (Supplementary Table 1). The most mutated genes were HEAT repeat containing 4 (*HEATR4*) (8 variants) and myosin heavy chain 7 (*MYH7*) (4 risk variants) and major histocompatibility complex, class II, DR beta 1 (*HLA-DRB1*) (3 risk variants). Comparing the four models for maximum LOD score achieved shows that R models are more "informative" (with more linkage information) than D models. The markers with the top LOD scores per model are shown in Fig. 6. Interestingly, two markers are within the same gene (*MYH7*).

All detected risk variants are novel, including those detected in established T2D risk genes. Of the 355 genes identified in our study, 341 (96%) are novel and have not been reported with T2D or any of its related phenotypes/traits (i.e., obesity, metabolic syndrome, insulin resistance, polycystic ovary syndrome, and hyperglycemia). The full list of detected intragenic variants is available in Supplementary Table 1.

3.1. In-silico analysis

Two hundred and fifty-five genome-wide-significant genes identified in our study clustered in several pathways related to metabolic functions (Gillespie et al., 2022). The topmost significant pathways are signal transduction (13%), metabolism (9%), immune system (9%), metabolism of proteins (8%), and disease (mostly related to carbohydrate metabolism) (7%). The pathways with more than 10 genes (3%) are shown in Fig. 7. And the full list of identified pathways is listed in Supplementary Table 2.

4. Discussion

Elucidating novel genes and pathways associated with the risk of T2D is pivotal to understand the diseases' pathogenesis, predict risks, and develop targeted therapies. In this study, we report several novel variants and genes significantly linked to and/or associated with the risk of T2D under genome-wide significance level. Our study constitutes the first familial T2D-linkage and association study in the Italian population. The risk alleles are equally distributed between major, less common, and minor alleles, thus supporting that both common, less common, and rare variants contribute to the risk of T2D, allowing for both a polygenic and oligogenic disease model underlying the disorder.

Our study replicated the previously reported association with T2D, in both similarly and different ethnic populations for the following genes: Janus kinase 2 (*JAK2*), EBF transcription factor 1 (*EBF1*), solute carrier family 22 member 3 *(SLC22A3),* thyrotropin releasing hormone receptor (*TRHR*), protein kinase AMP-activated non-catalytic subunit gamma

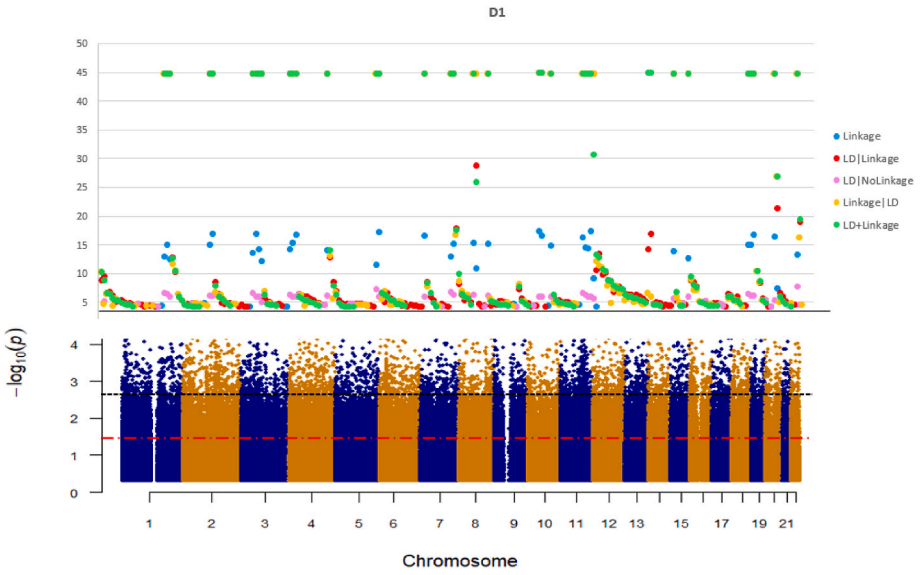

Fig. 1. Manhattan plot for genome-wide linkage to and linkage disequilibrium with T2D under the dominant model with complete penetrance (D1).
Legend. For each genomic-wide significant SNP in T2D in D1 (N = 247), we present the −log10(P) as a function of the significant test statistics [(Linkage, Linkage disequilibrium (LD)|Linkage, LD|NoLinkage, Linkage|LD and LD + Linkage)] per inheritance model. D1: dominant, complete penetrance. The dotted black line indicates level of suggestive significance ($P < 0.0017$), while the solid black line indicates level of genome-wide significance ($P < 0.0005$). The dashed red line indicates level of nominal significance. The upper graph shows the different test statistics for the genome-wide significant variants only ($P < 0.0005$). They are a magnification of the most significant variants. The aim of both these graphs is to show the genomic location (X axis) of the genome-wide significant variants (Y axis). Alternating blue and orange colors in the lower graph represent separate chromosomes. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

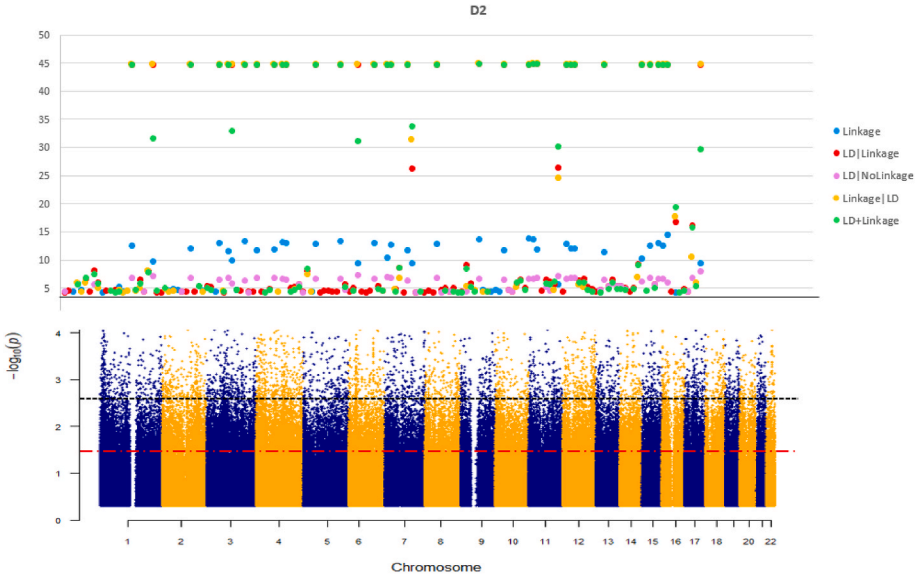

Fig. 2. Manhattan plot for genome-wide linkage to and linkage disequilibrium with T2D under the dominant model with incomplete penetrance (D2).
Legend. For each genomic-wide significant SNP in T2D in D2 (N = 152), we present the −log10(P) as a function of the significant test statistics [(Linkage, Linkage disequilibrium (LD)|Linkage, LD|NoLinkage, Linkage|LD and LD + Linkage)] per inheritance model. D2: dominant, incomplete penetrance. The dotted black line indicates level of suggestive significance ($P < 0.0017$), while the solid black line indicates level of genome-wide significance ($P < 0.0005$). The dashed red line indicates level of nominal significance. The upper graph shows the different test statistics for the genome-wide significant variants only ($P < 0.0005$). They are a magnification of the most significant variants. The aim of both these graphs is to show the genomic location (X axis) of the genome-wide significant variants (Y axis). Alternating blue and orange colors in the lower graph represent separate chromosomes. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

2 (*PRKAG2*), A-kinase anchoring protein 6 (*AKAP6*), hydroxysteroid 11-beta dehydrogenase 1 (*HSD11B1*), ectonucleotide pyrophosphatase/phosphodiesterase 1 (*ENPP1*), potassium voltage-gated channel subfamily C member 2 (*KCNC2*), alpha kinase 1 (*ALPK1*), HNF1 homeobox A (*HNF1A*), and *HLA-DRB*1 (Mahajan et al., 2018; Jing et al., 2012; Hwang et al., 2016; Chinniah et al., 2021; Devang et al., 2017; Shimokata et al., 2013; Zhang et al., 2022; Li et al., 2022). The *EBF1*, *SLC22A3*, *HNF1A*, *TRHR*, and *AKAP6* genes were previously reported in Caucasian patients with T2D (Mahajan et al., 2018; Voight et al., 2010), and the *PRKAG2, ALPK1, JAK2, ENPP1, KCNC2*, *HLA-DRB1*, and *HSD11B1*

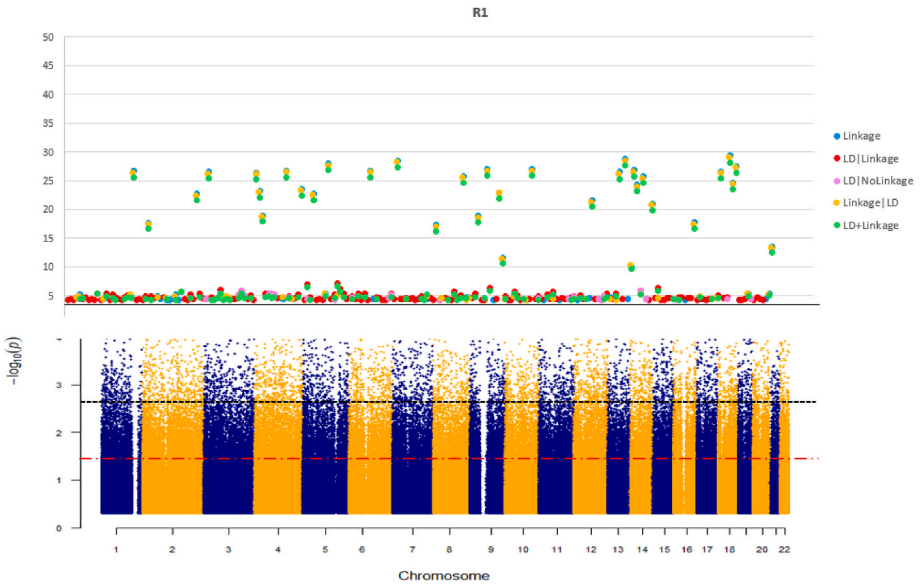

Fig. 3. Manhattan plot for genome-wide linkage to and linkage disequilibrium with T2D under the recessive model with complete penetrance (R1).
Legend. For each genomic-wide significant SNP in T2D in R1 (N = 235), we present the −log10(P) as a function of the significant test statistics [(Linkage, Linkage disequilibrium (LD)|Linkage, LD|NoLinkage, Linkage|LD and LD + Linkage)] per inheritance model. R1: recessive, complete penetrance. The dotted black line indicates level of suggestive significance (P < 0.0017), while the solid black line indicates level of genome-wide significance (P < 0.0005). The dashed red line indicates level of nominal significance. The upper graph shows the different test statistics for the genome-wide significant variants only (P < 0.0005). They are a magnification of the most significant variants. The aim of both these graphs is to show the genomic location (X axis) of the genome-wide significant variants (Y axis). Alternating blue and orange colors in the lower graph represent separate chromosomes. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

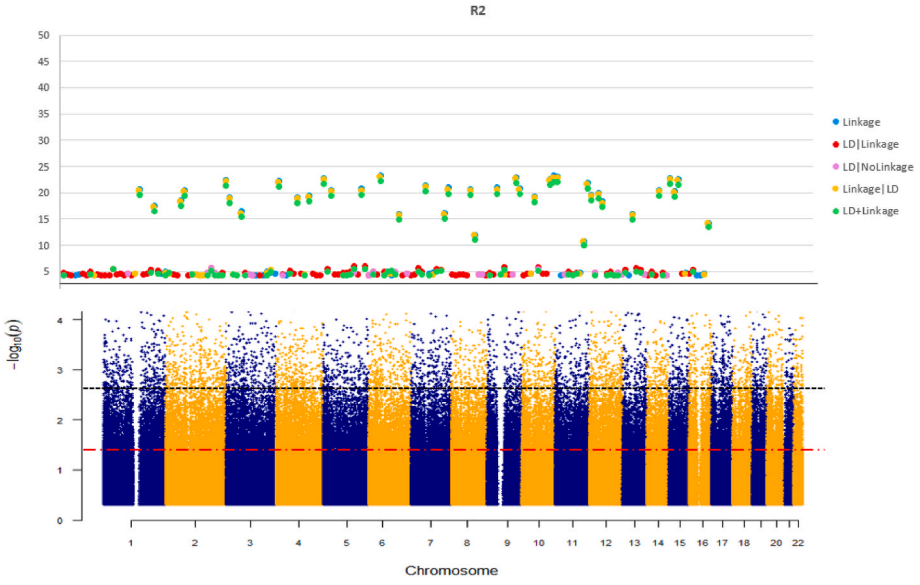

Fig. 4. Manhattan plot for genome-wide linkage to and linkage disequilibrium with T2D under the recessive model with incomplete penetrance (R2).
Legend. For each genomic-wide significant SNP in T2D in R2 (N = 171), we present the −log10(P) as a function of the significant test statistics [(Linkage, Linkage disequilibrium (LD)|Linkage, LD|NoLinkage, Linkage|LD and LD + Linkage)] per inheritance model. R2: recessive, incomplete penetrance. The dotted black line indicates level of suggestive significance (P < 0.0017), while the solid black line indicates level of genome-wide significance (P < 0.0005). The dashed red line indicates level of nominal significance. The upper graph shows the different test statistics for the genome-wide significant variants only (P < 0.0005). They are a magnification of the most significant variants. The aim of both these graphs is to show the genomic location (X axis) of the genome-wide significant variants (Y axis). Alternating blue and orange colors in the lower graph represent separate chromosomes. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

genes were reported in Tunisian (Nouira et al., 2010), Japanese (Shimokata et al., 2013), Chinese (Jing et al., 2012; Zhang et al., 2022), Korean (Hwang et al., 2016), and Indian (Chinniah et al., 2021; Devang et al., 2017) patients with T2D, respectively. The *HSD11B1* and engulfment and cell motility 1 (*ELMO1*) genes reported in our study have previously been associated with metabolic syndrome (Gandhi et al., 2013), obesity and insulin resistance (Stewart, 2003), and diabetic nephropathy (Wu et al., 2013), respectively, highlighting the possible bidirectional risks or better the underlying genetic comorbidity of these concomitant phenotypes.

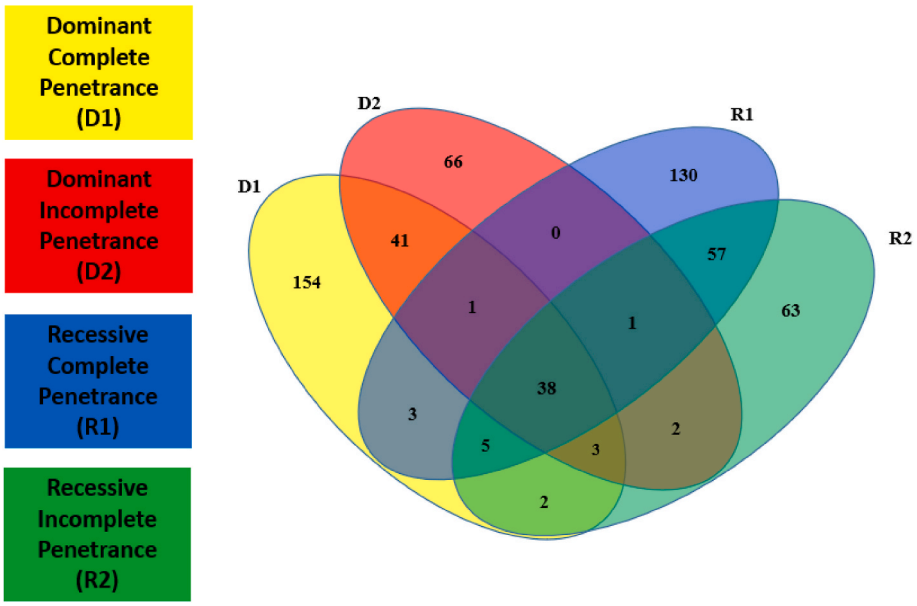

Fig. 5. Venn diagram showing number of genome-wide significant (P < 0.00005) variants under each model (D1, D2, R1, R2)
Legend. The number of genome-wide significant variants are reported if present only under D1, D2, R1, R2 models or if present under the combination of one, two, three, or four models.

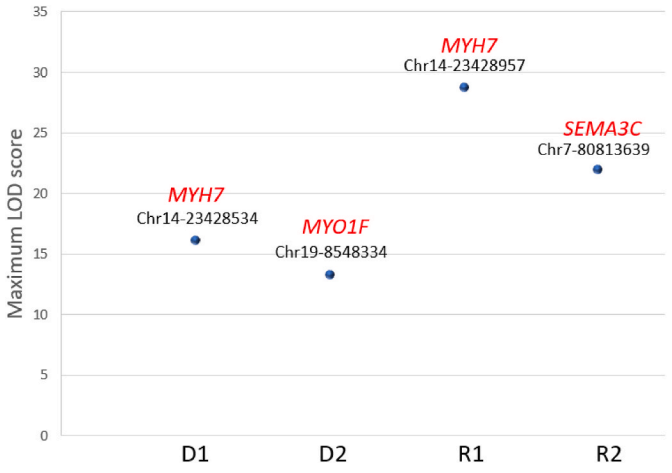

Fig. 6. Markers with maximum logarithm of the odds score (LOD) per each inheritance model.
Legend. D1: dominant, complete penetrance, D2: dominant, incomplete penetrance R1: recessive, complete penetrance R2: recessive, incomplete penetrance (*MYH7* = myosin heavy chain 7, *MYO1F* = myosin IF, *SEMA3C* = semaphorin 3C).

The remaining genes reported in our study are all novel and their functional relevance in the context of T2D is a critical aspect to explore. None of the variants reported in our study intersected with pancreatic islets regulatory elements (Pasquali et al., 2014), however several of the genes were found to play important regulatory roles in insulin signaling and/or β cell function. The growth factor receptor bound protein 14 (*GRB14*) gene controls insulin signaling and action (Gondoin et al., 2014), while the G protein-coupled receptor 142 (*GPR142*) gene stimulates the release from islets of glucagon-like peptide-1, which improves β cell function (Lin et al., 2018), and whose receptor agonist is used in T2D therapies (Lizarzaburu et al., 2012). The *RYR2* gene, encoding for the ryanodine receptor 2, a component of the family of ryanodine receptors forming calcium ion channel transporters, regulates insulin release and glucose homeostasis (Santulli et al., 2015), and the *NME7* gene modulates glucose tolerance in rats (Šedová et al., 2021). The phosphodiesterase 7B (*PDE7B*), nuclear receptor corepressor 2 (*NCoR2*), and paired box 5 (*PAX5*) genes are T2D-candidate genes since they encode important metabolic regulators (Pasquali et al., 2014; Paluvai et al., 2023; Bacos et al., 2023).

Some of the reported genes in our study are differentially expressed in T2D and/or its associated complications (e.g., ischemic heart disease [IHD]). Notably, the ATPase H+ transporting V1 subunit H (*ATP6V1H*) gene is down-regulated in T2D (Molina et al., 2011), and is a potential critical regulator of the development of T2D due to its vacuolar-ATPase activity, which is implicated in T2D (Molina et al., 2011; Lu et al., 2008). The *RYR2* and placenta associated 8 (*PLAC8)* genes are over-expressed in cardiomyocytes in concomitant T2D with IHD (Afanas'ev et al., 2021) and obese rats (Sasaki et al., 2015), respectively. The *PLAC8* gene is linked to gestational diabetes (GD) but with reverse causality (Blue et al., 2015). Intrauterine exposure to GDM causes epigenetic changes in the *PLAC8* gene (Blue et al., 2015), but to the best of our knowledge, no risk variants have been reported in T2D patients. The expression of contactin 5 (*CNTN5*) and cadherin 13 (*CDH13*) genes is associated respectively with variations in fructosamine levels (which measures short-term glycemic control) (Riveros-Mckay et al., 2022) and circulating adiponectin levels (Breitfeld et al., 2012).

The functional roles of the remaining novel variants and respective genes reported in our study are yet to be elucidated. Our *in-silico* analysis of the risk variants yielded no predicted results.

We used Reactome (Gillespie et al., 2022) to analyze the genes-sets for related pathways. We found that the genome-wide-significant genes identified in our study clustered in several pathways related to metabolic functions. The topmost significant pathways are signal transduction (13%), metabolism (9%), immune system (9%), metabolism of proteins (8%), and disease (mostly related to carbohydrate metabolism) (7%) (Supplementary Table 2). All pathways with 10 or more genes (2.9%) were previously associated with T2D (signal transduction (Bottini et al., 2004), metabolism (Galicia-Garcia et al., 2020), immune system (Prasad et al., 2020), protein metabolism (Sha et al., 2021), disease (Galicia-Garcia et al., 2020), post-translational protein modification (Yang et al., 2018), developmental biology (Christensen et al., 2019), gene expression/transcription (Vorotnikov et al., 2022), RNA polymerase II transcription (Vorotnikov et al., 2022), innate immune system (Zhou et al., 2018), metabolism of lipids (Silva et al.,

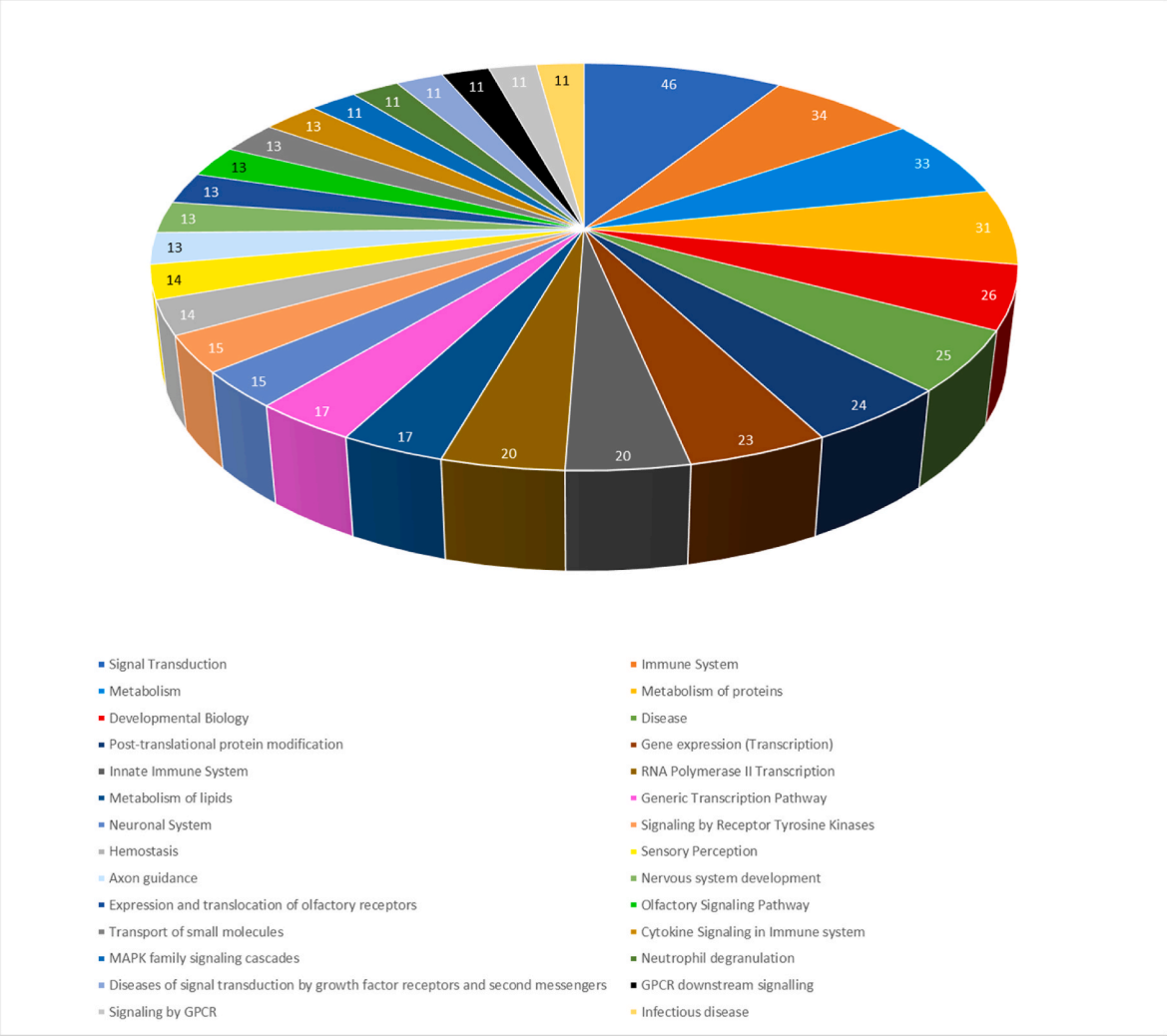

Fig. 7. Pathways analysis for genes genome-wide significantly linked to and/or associated with T2D ($P < 0.00005$).
Legend. We present the significant pathways for the genome-wide significantly variants linked to and/or associated with T2D ($P < 0.00005$) analyzed by Reactome. The figures in the pie chart represent and report gene-count per pathway.

2014), generic transcription pathway (Rui, 2014), transport of small molecules (Jaberi et al., 2021), neuronal system (Tumminia et al., 2018), hemostasis (Arsana et al., 2022), axon guidance (Satake et al., 2021), nervous system development (Lundqvist et al., 2019), signaling by receptor-tyrosine kinases (Majumder et al., 2019), cytokine signaling in immune system (Donath et al., 2019), sensory perception (Al-Rubeaan, 2021), G-protein coupled receptor-downstream signaling (Barella et al., 2021), expression and translocation of olfactory receptors (Shepard et al., 2019), and infectious disease (Carey et al., 2018)).

Of note, the mitogen-activated protein kinase 10 (*MAPK10*) gene is part of the pathway involved in hyperglycemia-induced myocardial infarction (Deng et al., 2022).

In conclusion, the findings presented in this article contribute valuable insights into potential mechanisms underlying T2D pathogenesis, opening doors for further research. Interestingly, the *GPR142* is a known potential target for the treatment of T2D (Guo et al., 2016) and obesity and reduction of cardiovascular risk (Strassheim et al., 2021), which paves the way for personalized approaches to T2D management.

Funding

This publication was partially supported by the funds received under Nebraska Laws 2021, LB 380, Section 109 awarded to C.G. (PI), Creighton University School of Medicine, through the Nebraska Department of Health & Human Services (DHHS). Its contents represent the views of the authors and do not necessarily represent the official views of the State of Nebraska or DHHS.

Ethics approval

Families were recruited following the Helsinki declaration guidelines, and individuals provided written informed consent prior to participation. The Bios Ethical Committee approved this study (Prot.PR/Mg/Cg/311708).

Data availability statement

The study data are available on reasonable request, and due to lacking specific patients' consent and privacy restrictions, they are not publicly available.

CRediT authorship contribution statement

Mutaz Amin: Writing – review & editing, Writing – original draft, Formal analysis. **Claudia Gragnoli:** Writing – review & editing, Writing – original draft, Supervision, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We thank the families who participated in the study, and we thank Bios Biotech Multi-Diagnostic Health Center, Rome, Italy, for data access and for financial, medical, and laboratory staff support.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amolm.2024.100046.

References

Afanas'ev, S.A., et al., 2021. Expression of genes and proteins of the sarcoplasmic reticulum ?a(2+)-transport systems in cardiomyocytes in concomitant coronary heart disease and type 2 diabetes mellitus. Bull. Exp. Biol. Med. 172 (2), 117–120.
Al-Rubeaan, K., et al., 2021. Hearing loss among patients with type 2 diabetes mellitus: a cross-sectional study. Ann. Saudi Med. 41 (3), 171–178.
Ali, O., 2013. Genetics of type 2 diabetes. World J. Diabetes 4 (4), 114–123.
Arsana, P.M., et al., 2022. Detection of hemostasis abnormalities in type 2 diabetes mellitus using thromboelastography. J ASEAN Fed Endocr Soc 37 (2), 42–48.
Bacos, K., et al., 2023. Type 2 diabetes candidate genes, including PAX5, cause impaired insulin secretion in human pancreatic islets. J. Clin. Invest. 133 (4).
Barella, L.F., et al., 2021. Metabolic roles of G protein-coupled receptor signaling in obesity and type 2 diabetes. FEBS J. 288 (8), 2622–2644.
Blue, E.K., et al., 2015. Epigenetic regulation of placenta-specific 8 contributes to altered function of endothelial colony-forming cells exposed to intrauterine gestational diabetes mellitus. Diabetes 64 (7), 2664–2675.
Bottini, N., et al., 2004. Type 2 diabetes and the genetics of signal transduction: a study of interaction between adenosine deaminase and acid phosphatase locus 1 polymorphisms. Metabolism 53 (8), 995–1001.
Breitfeld, J., Stumvoll, M., Kovacs, P., 2012. Genetics of adiponectin. Biochimie 94 (10), 2157–2163.
Carey, I.M., et al., 2018. Risk of infection in type 1 and type 2 diabetes compared with the general population: a matched cohort study. Diabetes Care 41 (3), 513–521.
Chelala, C., Khan, A., Lemoine, N.R., 2009. SNPnexus: a web database for functional annotation of newly discovered and public domain single nucleotide polymorphisms. Bioinformatics 25 (5), 655–661.
Chinniah, R., et al., 2021. HLA-DRB1 genes and the expression dynamics of HLA CIITA determine the susceptibility to T2DM. Immunogenetics 73 (4), 291–305.
Christensen, A.A., Gannon, M., 2019. The beta cell in type 2 diabetes. Curr. Diabetes Rep. 19 (9), 81.
Chung, W.K., et al., 2020. Precision medicine in diabetes: a consensus report from the American diabetes association (ADA) and the European association for the study of diabetes (EASD). Diabetes Care 43 (7), 1617–1635.
Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. National Diabetes Data Group. Diabetes 28 (12), 1979, 1039–1057.
DeForest, N., Majithia, A.R., 2022. Genetics of type 2 diabetes: implications from large-scale studies. Curr. Diabetes Rep. 22 (5), 227–235.
Dendup, T., et al., 2018. Environmental risk factors for developing type 2 diabetes mellitus: a systematic review. Int. J. Environ. Res. Publ. Health 15 (1).
Deng, Y.W., et al., 2022. Hyperglycemia promotes myocardial dysfunction via the ERS-MAPK10 signaling pathway in db/db mice. Lab. Invest. 102 (11), 1192–1202.
Devang, N., et al., 2017. Association of HSD11B1 gene polymorphisms with type 2 diabetes and metabolic syndrome in South Indian population. Diabetes Res. Clin. Pract. 131, 142–148.
Donath, M.Y., Dinarello, C.A., Mandrup-Poulsen, T., 2019. Targeting innate immune mediators in type 1 and type 2 diabetes. Nat. Rev. Immunol. 19 (12), 734–746.
Galicia-Garcia, U., et al., 2020. Pathophysiology of type 2 diabetes mellitus. Int. J. Mol. Sci. 21 (17).
Gandhi, K., et al., 2013. Association between a 11β-hydroxysteroid dehydrogenase type 1 gene polymorphism and metabolic syndrome in a South Indian population. Metab. Syndr. Relat. Disord. 11 (6), 397–402.
Gillespie, M., et al., 2022. The reactome pathway knowledgebase 2022. Nucleic Acids Res. 50 (D1), D687–d692.
Gondoin, A., et al., 2014. [Control of insulin signalisation and action by the Grb14 protein]. Biol Aujourdhui 208 (2), 119–136.
Grarup, N., et al., 2014. Genetic susceptibility to type 2 diabetes and obesity: from genome-wide association studies to rare variants and beyond. Diabetologia 57 (8), 1528–1541.
Guo, L., et al., 2016. Discovery and optimization of a novel triazole series of GPR142 agonists for the treatment of type 2 diabetes. ACS Med. Chem. Lett. 7 (12), 1107–1111.
Hemminki, K., et al., 2010. Familial risks for type 2 diabetes in Sweden. Diabetes Care 33 (2), 293–297.
Hiekkalinna, T., et al., 2011. PSEUDOMARKER: a powerful program for joint linkage and/or linkage disequilibrium analysis on mixtures of singletons and related individuals. Hum. Hered. 71 (4), 256–266.
Hwang, J.Y., et al., 2016. An integrative study identifies KCNC2 as a novel predisposing factor for childhood obesity and the risk of diabetes in the Korean population. Sci. Rep. 6, 33043.
Jaberi, S.A., et al., 2021. Lipocalin-2: structure, function, distribution and role in metabolic disorders. Biomed. Pharmacother. 142, 112002.
Jing, C., Xueyao, H., Linong, J., 2012. Meta-analysis of association studies between five candidate genes and type 2 diabetes in Chinese Han population. Endocrine 42 (2), 307–320.
Khan, M.A.B., et al., 2020. Epidemiology of type 2 diabetes – global burden of disease and forecasted trends. J. Epidemiology Global Health 10 (1), 107-107.
Kumar, S., Ambrosini, G., Bucher, P., 2017. SNP2TFBS - a database of regulatory SNPs affecting predicted transcription factor binding site affinity. Nucleic Acids Res. 45 (D1), D139–d144.
Kwak, S.H., Park, K.S., 2016. Recent progress in genetic and epigenetic research on type 2 diabetes. Exp. Mol. Med. 48 (3), e220.
Laakso, M., Fernandes Silva, L., 2022. Genetics of type 2 diabetes: past, present, and future. Nutrients 14 (15).
Li, L.M., Jiang, B.G., Sun, L.L., 2022. HNF1A:From monogenic diabetes to type 2 diabetes and gestational diabetes mellitus. Front. Endocrinol. 13, 829565.
Lin, H.V., et al., 2018. GPR142 prompts glucagon-like Peptide-1 release from islets to improve β cell function. Mol. Metabol. 11, 205–211.
Lizarzaburu, M., et al., 2012. Discovery and optimization of a novel series of GPR142 agonists for the treatment of type 2 diabetes mellitus. Bioorg. Med. Chem. Lett 22 (18), 5942–5947.
Lu, H., et al., 2008. The identification of potential factors associated with the development of type 2 diabetes: a quantitative proteomics approach. Mol. Cell. Proteomics 7 (8), 1434–1451.
Lundqvist, M.H., et al., 2019. Is the brain a key player in glucose regulation and development of type 2 diabetes? Front. Physiol. 10, 457.
Mahajan, A., et al., 2018. Fine-mapping type 2 diabetes loci to single-variant resolution using high-density imputation and islet-specific epigenome maps. Nat. Genet. 50 (11), 1505–1513.
Majumder, P., et al., 2019. Receptor tyrosine kinases (RTKs) consociate in regulatory clusters in Alzheimer's disease and type 2 diabetes. Mol. Cell. Biochem. 459 (1–2), 171–182.
Meigs, J.B., 2019. The genetic epidemiology of type 2 diabetes: opportunities for health translation. Curr. Diabetes Rep. 19 (8), 62.
Molina, M.F., et al., 2011. Decreased expression of ATP6V1H in type 2 diabetes: a pilot report on the diabetes risk study in Mexican Americans. Biochem. Biophys. Res. Commun. 412 (4), 728–731.
Murea, M., Ma, L., Freedman, B.I., 2012. Genetic and environmental factors associated with type 2 diabetes and diabetic vascular complications. Rev. Diabet. Stud. : Reg. Dev. Stud. 9 (1), 6-6.
Nouira, S., et al., 2010. Identification of two novel variants in PRKAG2 gene in Tunisian type 2 diabetic patients with family history of cardiovascular disease. Diabetes Res. Clin. Pract. 87 (2), e7–e10.
Nyenwe, E.A., et al., 2011. Management of type 2 diabetes: evolving strategies for the treatment of patients with type 2 diabetes. Metabolism 60 (1), 1–23.
Paluvai, H., et al., 2023. Insights into the function of HDAC3 and NCoR1/NCoR2 co-repressor complex in metabolic diseases. Front. Mol. Biosci. 10, 1190094.
Pasquali, L., et al., 2014. Pancreatic islet enhancer clusters enriched in type 2 diabetes risk-associated variants. Nat. Genet. 46 (2), 136–143.
Prasad, R.B., Groop, L., 2015. Genetics of type 2 diabetes-pitfalls and possibilities. Genes 6 (1), 87–123.
Prasad, M., et al., 2020. Autoimmune responses and inflammation in type 2 diabetes. J. Leukoc. Biol. 107 (5), 739–748.
Purcell, S., et al., 2007. PLINK: a tool set for whole-genome association and population-based linkage analyses. Am. J. Hum. Genet. 81 (3), 559–575.
Riveros-Mckay, F., et al., 2022. An expanded genome-wide association study of fructosamine levels identifies RCN3 as a replicating locus and implicates FCGRT as the effector transcript. Diabetes 71 (2), 359–364.
Rui, L., 2014. Energy metabolism in the liver. Compr. Physiol. 4 (1), 177–197.
Santulli, G., et al., 2015. Calcium release channel RyR2 regulates insulin release and glucose homeostasis. J. Clin. Invest. 125 (5), 1968–1978.
Sasaki, D., et al., 2015. New animal models reveal that coenzyme Q2 (Coq2) and placenta-specific 8 (Plac8) are candidate genes for the onset of type 2 diabetes associated with obesity in rats. Mamm. Genome 26 (11–12), 619–629.
Satake, E., et al., 2021. Comprehensive search for novel circulating miRNAs and axon guidance pathway proteins associated with risk of ESKD in diabetes. J. Am. Soc. Nephrol. 32 (9), 2331–2351.
Šedová, L., et al., 2021. Heterozygous Nme7 mutation affects glucose tolerance in male rats. Genes 12 (7).
Sha, W., et al., 2021. Mechanism of ferroptosis and its role in type 2 diabetes mellitus. J. Diabetes Res. 2021, 9999612.
Shepard, B.D., Koepsell, H., Pluznick, J.L., 2019. Renal olfactory receptor 1393 contributes to the progression of type 2 diabetes in a diet-induced obesity model. Am. J. Physiol. Ren. Physiol. 316 (2), F372–f381.
Shimokata, S., et al., 2013. Association between polymorphisms of the α-kinase 1 gene and type 2 diabetes mellitus in community-dwelling individuals. Biomed Rep 1 (6), 940–944.

Shojima, N., Yamauchi, T., 2023. Progress in genetics of type 2 diabetes and diabetic complications. J Diabetes Investig 14 (4), 503–515.
Silva, V.M., et al., 2014. Plasma lipids, lipoprotein metabolism and HDL lipid transfers are equally altered in metabolic syndrome and in type 2 diabetes. Lipids 49 (7), 677–684.
Stewart, P.M., 2003. Tissue-specific Cushing's syndrome, 11beta-hydroxysteroid dehydrogenases and the redefinition of corticosteroid hormone action. Eur. J. Endocrinol. 149 (3), 163–168.
Strassheim, D., et al., 2021. Metabolite G-protein coupled receptors in cardio-metabolic diseases. Cells 10 (12).
Tumminia, A., et al., 2018. Type 2 diabetes mellitus and Alzheimer's disease: role of insulin signalling and therapeutic implications. Int. J. Mol. Sci. 19 (11).
Voight, B.F., et al., 2010. Twelve type 2 diabetes susceptibility loci identified through large-scale association analysis. Nat. Genet. 42 (7), 579–589.
Vorotnikov, A.V., Popov, D.V., Makhnovskii, P.A., 2022. Signaling and gene expression in skeletal muscles in type 2 diabetes: current results and OMICS perspectives. Biochemistry (Mosc.) 87 (9), 1021–1034.
Wu, H.Y., et al., 2013. Association of ELMO1 gene polymorphisms with diabetic nephropathy in Chinese population. J. Endocrinol. Invest. 36 (5), 298–302.
Xu, Z., Taylor, J.A., 2009. SNPinfo: integrating GWAS and candidate gene information into functional SNP selection for genetic association studies. Nucleic Acids Res. 37 (Suppl. 2).
Xue, A., et al., 2018. Genome-wide association analyses identify 143 risk variants and putative regulatory mechanisms for type 2 diabetes. Nat. Commun. 9 (1), 2941.
Yang, Q., Vijayakumar, A., Kahn, B.B., 2018. Metabolites as regulators of insulin sensitivity and metabolism. Nat. Rev. Mol. Cell Biol. 19 (10), 654–672.
Zhang, Y., et al., 2022. Association analysis of SOCS3, JAK2 and STAT3 gene polymorphisms and genetic susceptibility to type 2 diabetes mellitus in Chinese population. Diabetol. Metab. Syndrome 14 (1), 4.
Zhou, T., et al., 2018. Role of adaptive and innate immunity in type 2 diabetes mellitus. J. Diabetes Res. 2018, 7457269.