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Novel TCF7L2 familial linkage and association with Type 2 diabetes, depression, and their comorbidity

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Abstract. – OBJECTIVE: Alterations in the activity of the transcription factor 7-like 2 (TCF7L2) generate defects previously associated with neuropsychiatric disorders. We investigated the role of the TCF7L2 gene in major depressive disorder (MDD), type 2 diabetes (T2D), and MDD-T2D comorbidity. We tested whether TCF7L2 is in linkage to and/or in linkage disequilibrium (LD, namely association) with MDD, T2D, and MDD-T2D.

PATIENTS AND METHODS: In 212 families with T2D and MDD in the Italian population, we analyzed 80 microarray-based SNPs using Pseudomarker software for linkage to and LD with T2D and MDD under the recessive model with complete penetrance (R1). In a secondary analysis, we tested the variants under the dominant models with complete penetrance (D1), recessive with incomplete penetrance (R2), and recessive with incomplete penetrance (R2).

RESULTS: We found several novel linkage signals and genetic associations. In addition, we found two new transcription-factor (TF) binding sites created by two risk variants found: the MDD-risk variant rs12255179 creates a new TF-binding site for the CCAAT/enhancer-binding protein α (C/EBPα), and the T2D-risk variant rs61872794 creates a new TF-binding site for the organic cation-uptake transporter (OCT1). Both new binding sites are related to insulin metabolism.

CONCLUSIONS: These results highlight the cross-interactivity between T2D and MDD. Further replication is needed in diverse ethnic groups.

Key Words:
Major depressive disorder, MDD, Depression, Type 2 diabetes, T2D, Transcription factor 7-like 2, TCF7L2, Linkage, Linkage disequilibrium, LD, Association, LD block, Comorbid, Mental-metabolic comorbidity, Pleiotropy, Gene, Variant, Single nucleotide polymorphism, SNP, Italian, Families, Schizophrenia, SCZ, Bipolar disorder, Microarray, PLINK, Pseudomarker, recessive, Dominant, model, Complete penetrance, Incomplete penetrance, In silico analysis, Tuscany, Independent, MRNA, Expression, Wnt signaling pathway, DSM-IV criteria, Intronic, Rs10885398, Rs11196181, Rs7903146, Rs11592706, Rs74825300, Rs4918788, Rs7919409, Rs12255179, Rs79805154, Rs3814572, Rs75351685, Rs7084875, Rs176632, Rs10885398, Rs10885401, Rs7904519, Rs10787472, Rs74825300, Rs11592706, Rs77795162, Rs61872787, Rs61872794, Rs6585205, Rs6585206,

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Rs7081841, Rs7084875, Rs112775103, CCAAT/Enhancer-Binding Protein α, C/EBPĐ, Lipid, Glucose metabolism, Triglycerides, Insulin resistance, Transcription factor, TF, Binding site, Organic cation-uptake transporter, OCT1, Type 1 diabetes, T1D, Obesity, Gestational diabetes, GD, Metabolic syndrome, MetS, Diabetic nephropathy, Cancer, Cystic fibrosis, CF, Premature adrenarche, Polycystic ovarian syndrome, PCOS, Cardiovascular disease, CVD, Coronary artery disease, CAD, Schizoid disorders, Effect, Neurogenesis, Oligodendrogenesis, Thalamocortical circuitry, Habenula, Developmental events, Molecular neuron diversification, Prosomere 2, In vivo, Ventral habenula formation, Functional activity, Ventral habenular neurons, Lateralized fate selection, Alternative pathways, major neural circuit asymmetries, Disintegration, Left thalamus, Right habenula tract function, Compensational mechanism, Familial study, Italy, Novel, Risk, First, Replicate, Ethnic groups, Role, Đ-Catenin, Pathway, Drug development.

Introduction

Major depressive disorder (MDD) and type 2 diabetes (T2D) are prevalent complex comorbid disorders that share many pathogenic mechanisms[1,2]. MDD confers a 60% increased risk for T2D in antidepressant-naïve patients[3]. Conversely, T2D is associated with a modest increase in MDD, with the latter appearing to be driving the increased MDD-T2D comorbidity risk[3]. It is possible that reciprocal association between depression and T2D may be due to common molecular determinants[1]. Also, it is hypothesized that depression may drive T2D risk based on shared genetic pathways[4].

The transcription factor 7-like 2 (TCF7L2), an essential component of the Wnt-signaling pathway, is the first and strongest T2D-genetic risk factor to be identified by linkage studies[5]. The genetic association of *TCF7L2* common variants with T2D is one of the most powerful discoveries in complex diseases. It has been consistently replicated in multiple populations with diverse genetic origins[5]. Furthermore, alterations in the activity of TCF7L2 generate defects previously associated with neuropsychiatric disorders[2]. Changes in the expression level of *TCF7L2* mRNA are part of the module associated with depression, and genetic analyses of *TCF7L2* have shown that the gene is involved in pathological processes that cause mental disorders[6] such as schizophrenia (SCZ)[7,8] and bipolar disorder[9,10]. The molecular mechanisms involved in this process are not well known[11,12].

In a mouse model, Savic et al[13] identified a role for *TCF7L2* in anxiety-like behavior and a dose-dependent effect of *TCF7L2* alleles on fear conditioning; when *TCF7L2* was ablated, fear learning increased and when *TCF7L2* was overexpressed, it was impaired. Interestingly, these differences were observed prior to the onset of detectable glucose metabolism abnormalities[13].

In this study, we aimed to test whether the *TCF7L2* gene plays a role in familial MDD, T2D, and MDD-T2D and whether it confers a potential risk for the genetic comorbidity of these clinically associated disorders.

Patients and Methods

In 212 Italian families diagnosed with T2D with extended family history[14,15] and phenotyped for MDD according to DSM-IV criteria[16], we analyzed 80 microarray-based single nucleotide polymorphisms (SNPs) in the *TCF7L2* gene, namely 76 intronic SNPs, 1 exonic SNP, 2 3'-UTR SNPs, and 1 synonymous SNP. The data that we accessed were fully deidentified.

Statistical Analysis

We excluded genotyping and Mendelian errors by PLINK (Available at: https://zzz.bwh.harvard.edu/plink/). We used Pseudomarker to analyze *TCF7L2*-variants for linkage to and linkage disequilibrium (LD, namely linkage + association) with T2D and MDD under the recessive model with complete penetrance (R1). In a secondary analysis, we tested the variants under the dominant models with complete penetrance (D1), recessive with incomplete penetrance (R2), and recessive with incomplete penetrance (R2). We then tested statistically significant SNPs ($p \leq 0.05$) for the presence or absence of LD blocks in the Tuscany Italian population from the 1,000 Genomes Project (Available at: https://www.internationalgenome.org/data-portal/population/TSI). SNPs were either "independent" or linked in a specific designated LD block (set01, set02, etc.). The Bios Ethical Committee approved the study.

Results

Based on our analysis, we identified the risk variants with statistical significance ($p \leq .05$) in MDD and/or T2D (Table I). In all, we found

that 10 unique variants conferred MDD risk; 10 unique variants conferred T2D risk; and 4 variants were comorbid (i.e., conferred MDD-T2D risk). The MDD risk variants 10-112996282-A-T and rs7903146 appeared within the same and sole MDD LD block (set01). The T2D risk variants, rs7904519 and rs10787472 appeared within the same and sole T2D LD block (set02). Variants within the same LD block function as replicates of one another.

Figure 1 shows the SNPs in linkage and/or LD with MDD, and Figure 2 shows the SNPs in linkage and/or LD with T2D. Figure 3 shows the MDD- and T2D-risk variants and the MDD-T2D comorbid variants. Several significant SNPs overlapped across the models (Table I). Venn diagrams show the overlapping MDD risk (Figure 4) and T2D risk (Figure 5) SNPs.

In Silico Analysis

We used the following tools to analyze the non-coding intronic variants for transcription factor (TF) binding: TFsearch (Available at: http://diyhpl.us/~bryan/irc/protocol-online/protocol-cache/TFSEARCH.html), SNP Function Prediction[20] (Available at: https://snpinfo.niehs.nih.gov/snpinfo/snpfunc.html), RegulomeDB[20] (Available at: https://regulomedb.org/regulome-search/), and SNPnexus[21] (Available at: https://www.snp-nexus.org/v4/). Predictions of splicing and miRNA binding were performed using SpliceAI[22] (Available at: https://spliceailookup.broadinstitute.org) and mirSNP[23] (Available at: https://ccb-compute.cs.uni-saarland.de/mirsnp), respectively. We found that the risk allele (C) of the MDD-risk variant rs12255179 creates a new TF-binding site for the CCAAT/Enhancer-Binding Protein α (C/EBPα), which regulates genes involved in lipid and glucose metabolism. C/EBPα is associated with elevated triglycerides[24], which might be mediated by insulin resistance. We also found that the risk allele (G) of the T2D-risk variant rs61872794 creates a new TF-binding site for the organic cation-uptake transporter (OCT1). OCT1 is a sensor of metabolic and stress signals and regulates insulin secretion in pancreatic beta cells[25]. These results highlight the cross interactivity between T2D and MDD.

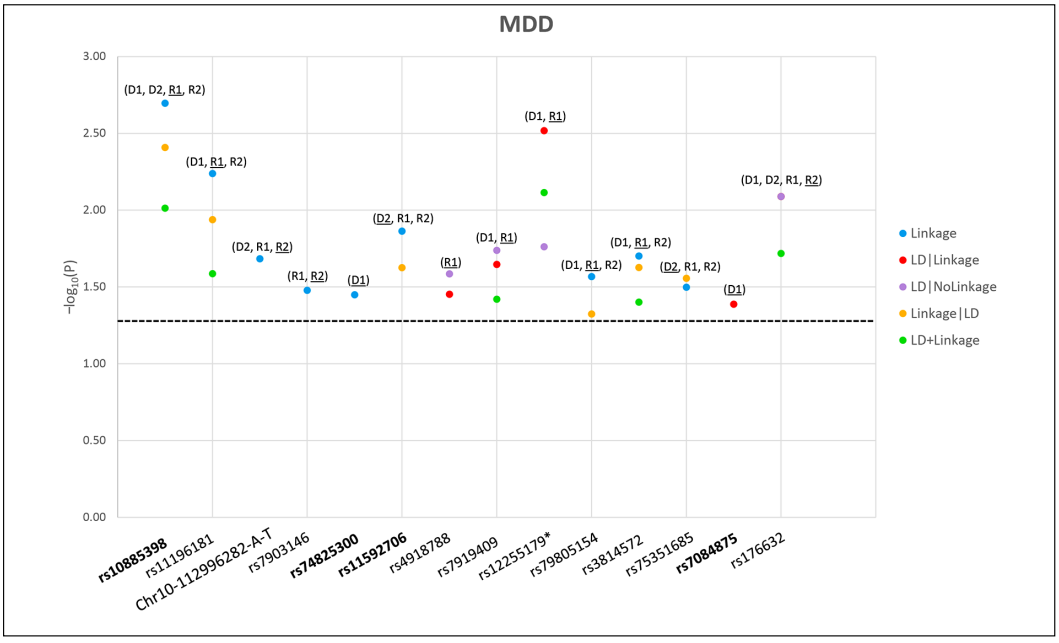

Figure 1. Linkage and linkage disequilibrium (i.e., association) of TCF7L2-risk single nucleotide polymorphisms (SNPs) in major depressive disorder using different inheritance models. For each TCF7L2-risk SNP in major depressive disorder (MDD), we presented the -$\log_{10}$ (p) as a function for each significant test statistic (Linkage, LD - Linkage, LD- No Linkage, Linkage - LD, and LD+Linkage). The most significant model is underlined. Per the inheritance model: D1: dominant, complete penetrance; D2: dominant, incomplete penetrance; R1: recessive, complete penetrance; R2: recessive, incomplete penetrance (*variant predicted to affect transcription-factor binding).

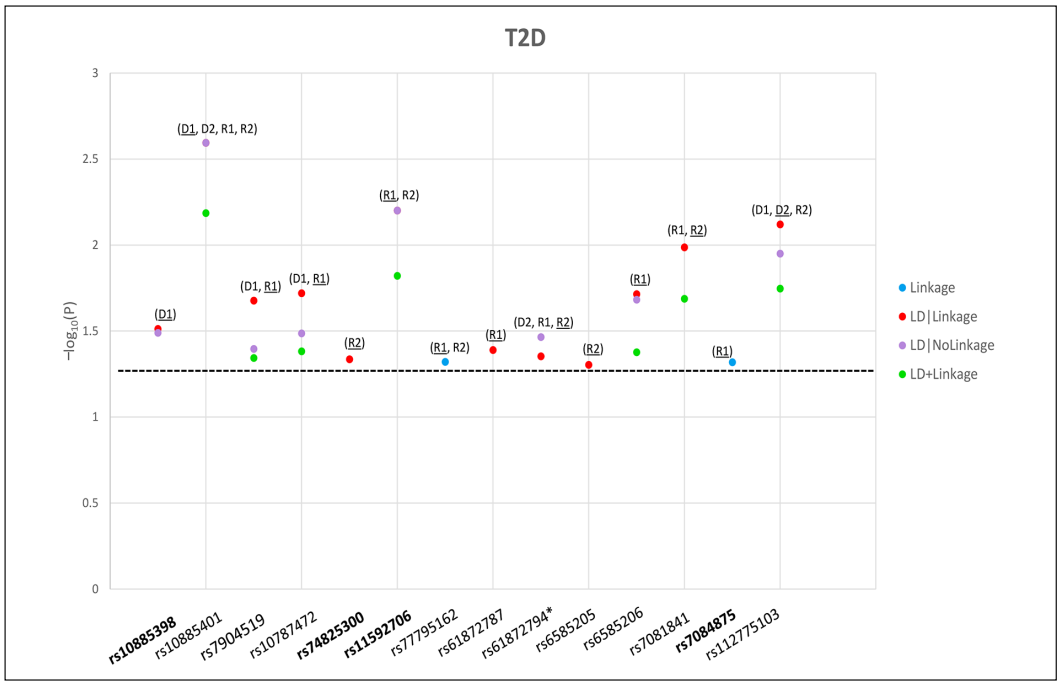

Figure 2. Linkage and linkage disequilibrium (i.e., association) of TCF7L2-risk single nucleotide polymorphisms (SNPs) in type 2 diabetes using different inheritance models. For each TCF7L2-risk SNP in type 2 diabetes (T2D), we presented the -$\log_{10}$ (p) as a function for each significant test statistic (Linkage, LD - Linkage, LD- No Linkage, Linkage - LD, and LD+Linkage). The most significant model is underlined. Per the inheritance model: D1: dominant, complete penetrance; D2: dominant, incomplete penetrance; R1: recessive, complete penetrance; R2: recessive, incomplete penetrance (*variant predicted to affect transcription-factor binding).

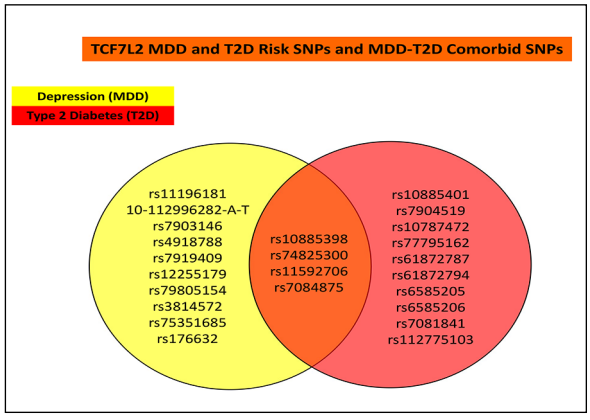

Figure 3. *TCF7L2* major depressive disorder (MDD) and type 2 diabetes (T2D) risk single nucleotide polymorphisms (SNPs) and MDD-T2D comorbid risk SNPs.

Discussion

Intronic variants in the Wnt-signaling pathway effector *TCF7L2* were reported[17] to be associated with the risk of T2D more than a decade ago. The contribution of *TCF7L2* to T2D risk was then confirmed *via* association studies[5] in numerous follow-up reports involving different ethnic groups. The rs7903146 variant is the most replicated T2D risk variants[17]. In addition, it appears to contribute to several diseases and diverse metabolic phenotypes[5,26].

Previously, two *TCF7L2* variants have been variably associated with schizoid disorders and T2D in SCZ (e.g., rs7903146, rs12573128) in African-Americans, Arab-Israeli families, and Danish populations[7,8,27]. In this study, among the published *TCF7L2* risk variants, we replicated only the T2D and SCZ risk intronic variant rs7903146 and in depression only[8,17]. We found it in linkage with depression (p = .048/R1, C allele, p = .033/R2, C allele). This finding indicates an intricate molecular cross section between MDD and T2D.

In addition to SCZ and T2D in SCZ patients, the MDD-rs7903146 risk variant reported in our study has also been associated with several other diseases, including type 1 diabetes[28-31], obesity[32-34], gestational diabetes[35], metabolic syndrome[36-38], diabetic nephropathy[39,40], diverse types of cancers[41-50], cystic fibrosis[51,52],

Table I. TCF7L2-risk single nucleotide polymorphisms for major depressive disorder risk and type 2 diabetes.

Disease	Model[1]	SNP	Chr10 Position	Ref	Alt	Risk Allele	Consequence	LD Block	Reported in MDD or T2D
MDD	D1, D2, R1, R2	rs10885398	112956171	A	G	G	Intronic	Independent	
	D1, R1, R2	rs11196181	112989259	G	A	G	Intronic	Independent	
	D2, R1, R2	-	112996282	A	T	A	Intronic	Set01	
	R1, R2	rs7903146	112998590	C	T	C	Intronic	Set01	T2D17
	D1	rs74825300	113030349	C	T	C	Intronic	Independent	
	D2, R1, R2	rs11592706	113039227	C	T	C	Intronic	Independent	
	R1	rs4918788	113061202	G	A	G	Intronic	Independent	
	D1, R1	rs7919409	113065217	C	T	T	Intronic	Independent	
	D1, R1	rs12255179	113069936	T	C	C	Intronic	Independent	
	D1, R1, R2	rs79805154	113083531	A	G	A	Intronic	Independent	
	D1, R1, R2	rs3814572	113087964	A	G	G	Intronic	Independent	
	D2, R1, R2	rs75351685	113095273	G	A	A	Intronic	Independent	
	D1	rs7084875	113110033	G	A	A	Intronic	Independent	
	D1, D2, R1, R2	rs176632	113151320	T	C	C	Intronic	Independent	
T2D	D1	rs10885398	112956171	A	G	G	Intronic	Independent	
	D1, D2, R1, R2	rs10885401	112986915	T	C	C	Intronic	Independent	
	D1, R1	rs7904519	113014168	A	G	A	Intronic	Set02	T2D18
	D1, R1	rs10787472	113021538	A	C	A	Intronic	Set02	T2D19
	R2	rs74825300	113030349	C	T	C	Intronic	Independent	
	R1, R2	rs11592706	113039227	C	T	C	Intronic	Independent	
	R1, R2	rs77795162	113049390	C	T	C	Intronic	Independent	
	R1	rs61872787	113053201	A	G	A	Intronic	Independent	
	D2, R1, R2	rs61872794	113070646	A	G	G	Intronic	Independent	
	R2	rs6585205	113099405	G	T	G	Intronic	Independent	
	R1	rs6585206	113099492	A	G	A	Intronic	Independent	
	R1, R2	rs7081841	113099657	C	G	C	Intronic	Independent	
	R1	rs7084875	113110033	G	A	A	Intronic	Independent	
	D1, D2, R2	rs112775103	113153279	T	G	T	Intronic	Independent	

[1]Models: D1: dominant complete-penetrance, D2: dominant incomplete-penetrance, R1: recessive complete-penetrance, R2: recessive incomplete-penetrance. The SNPs in bold are comorbid MDD-T2D risk variants. SNP, single nucleotide polymorphism; Chr, chromosome; Ref, reference; Alt, alternative; LD, linkage disequilibrium; MDD, major depressive disorder; T2D, type 2 diabetes.

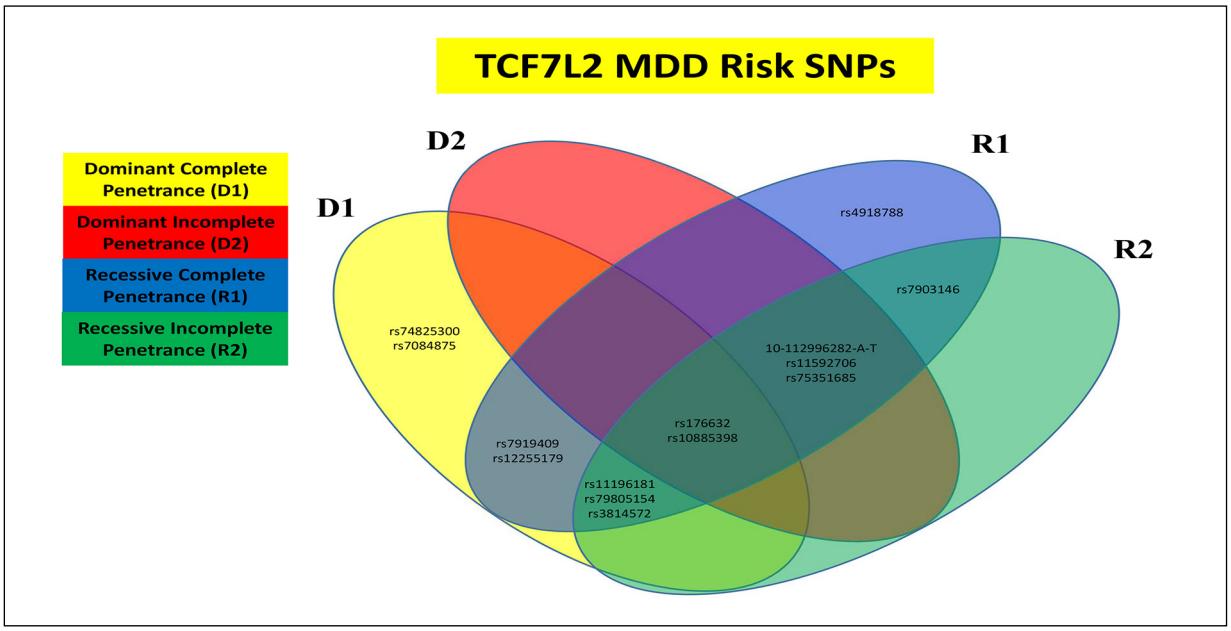

Figure 4. *TCF7L2* major depressive disorder (MDD) and risk variants across models in a Venn diagram.

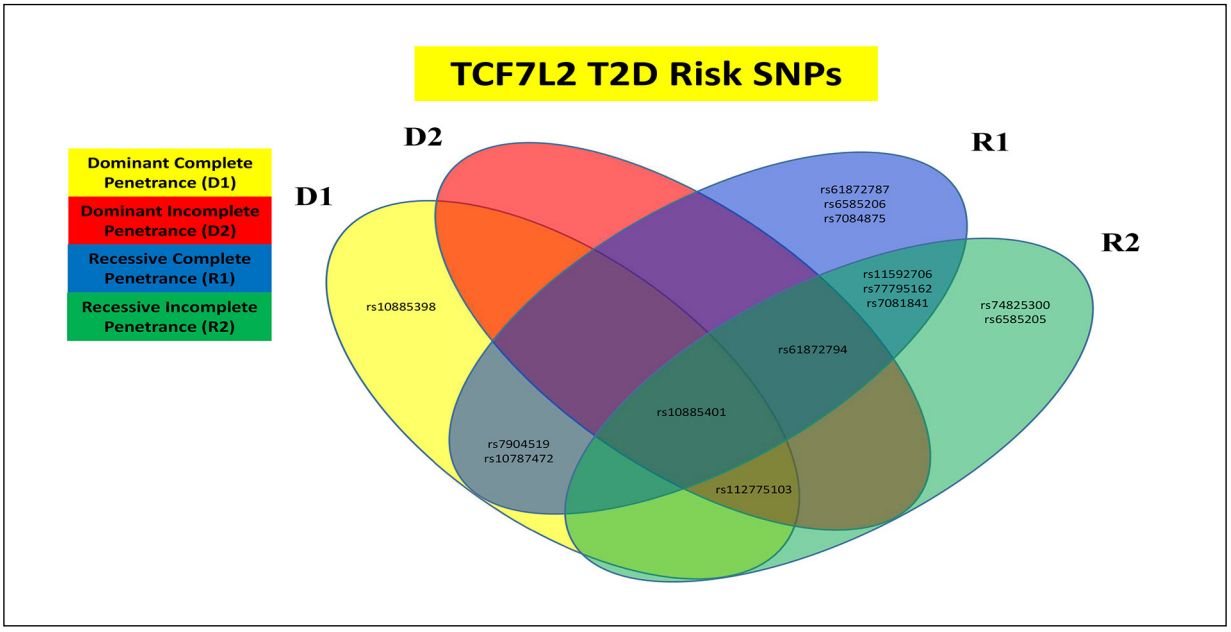

Figure 5. *TCF7L2* type 2 diabetes (T2D) and risk variants across models in a Venn diagram.

premature adrenarche[53], polycystic ovarian syndrome[54], and cardiovascular disease[55-57]. As the previously reported[8,17] T2D and schizoid risk variant rs7903146 and the MDD-risk variant of chromosome 10, 10-112996282-A-T are within the same MDD-only LD block set01; we can infer that these variants across different populations might confer risk for T2D, schizoid disorders, and MDD. We can also infer that they may have a pleiotropic effect. These mentioned variants within the LD block set01 and T2D risk variants rs7904519 and rs10787472 within the T2D LD block set02 function as replicates of each other.

We found 14 variants in linkage and/or as-

sociation with T2D. Of those, rs7904519 and rs10787472 recently have been reported[18,19] in T2D to have novel pleiotropic effects with coronary artery disease[18] and obesity[19], respectively.

It has been proposed[58] that TCF7L2 impairments disrupt neurogenesis, oligodendrogenesis, and the function of the thalamocortical circuitry and habenula. *In vivo*, during ventral habenula formation, functional TCF7L2 activity is required, and in its absence, ventral habenular neurons do not develop[59]. TCF7L2 is essential for lateralized fate selection by habenular neurons that can differentiate along two alternative pathways, thereby leading, if impaired, to major neural circuit asymmetries[6]. Of note, MDD is related to the disintegration of the left thalamus-right habenula tract function with the formation of an increased number of tracts as a compensational mechanism[60].

Conclusions

Using a familial study focused on families originating from Italy, we have discovered novel *TCF7L2* T2D and depression risk variants and we have replicated in depression the T2D and SCZ risk rs7903146 variant. This is the first study reporting *TCF7L2* variants in linkage to and LD with familial depression.

It is necessary to replicate our study variants reported in LD, namely association, in an additional Italian and other ethnic groups, investigating their role in depression and other T2D-comorbid disorders (i.e., SCZ) in other ethnic groups.

Of note, the β-catenin-*TCF7L2* pathway is related to various diseases, including SCZ. In the field of drug development, several efforts are currently underway to influence the β-catenin-*TCF7L2* pathway[61,62]. If our findings are replicated, this pathway may be a target for intervention in individuals or families with T2D and/or schizoid diseases, and/or potentially depression.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Contribution to the Field

Major depressive disorder (MDD) and type 2 diabetes (T2D) are prevalent complex, multifactorial disorders and sometimes comorbid. To explore whether this clinical association may be due to common molecular determinants, we analyzed genetic variations in TCF7L2, a fundamental component of the Wnt-signaling pathway, as common variants in this gene represent one of the most important discoveries in complex diseases consistently replicated in multiple populations. We tested whether TCF7L2 is linked to and/or in linkage disequilibrium with MDD, T2D, and MDD-T2D in Italian families with T2D and MDD, conferring a potential genetic predisposition for MDD-T2D comorbidity. We found 10 unique variants conferring MDD-risk, 10 unique variants conferring T2D-risk, and 4 variants comorbid that appear to grant MDD-T2D risk. Interestingly, in silico analysis showed that MDD-risk variant rs12255179 creates a new transcription factor (TF)-binding site for the CCAAT/Enhancer-Binding α, which regulates genes involved in lipid and glucose metabolism. Furthermore, the T2D-risk variant rs61872794 creates a new TF-binding site for the organic cation-uptake transporter, a sensor of metabolic and stress signals that regulate insulin secretion in beta cells. These results highlight cross interactivity between T2D and MDD and contribute to an innovative field, however further validation in diverse ethnic groups is necessary.

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Ethics Approval

Families were recruited following the Helsinki declaration guidelines. The Bios Ethical Committee approved this study.

Informed Consent

Individuals provided written informed consent prior to participation.

Authors' Contribution

C.G. conceived and supervised the project, including statistical analysis and manuscript drafting. L.D.B.P. helped with literature search, data assignments, and manuscript drafting. M.A. helped with the bioinformatic analysis and manuscript drafting. R.W. and T.T.P. critically helped in data interpretation and critical revision of the manuscript. All authors approved the final manuscript.

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Availability of Data and Materials

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

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