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Novel linkage and association of the mineralocorticoid receptor gene (*NR3C2)* with familial type 2 diabetes and depression and their comorbidity

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ABSTRACT

Introduction: The mineralocorticoid receptor gene (*NR3C2)* appears to modulate stress and cognitive performance in patients with major depressive disorder (MDD). In addition, abnormalities in *NR3C2* are associated in rodents with type 2 diabetes (T2D) and in humans with features of metabolic syndrome. Of note, NR3C2 antagonists are approved treatments in heart failure and chronic kidney disease with T2D. The *NR3C2* gene is therefore a candidate gene for studying T2D-MDD comorbidity. To our knowledge, no study has so far reported risk variants in the *NR3C2* gene with either MDD and/or T2D.
Materials and methods: In 212 multigenerational Italian families with enriched family history of T2D and with MDD, we analyzed 86 single nucleotide polymorphisms (SNPs) within the *NR3C2* gene for parametric linkage to and/or linkage disequilibrium (LD) with T2D and MDD.
Results: We identified a total of 7 independent SNPs significantly linked to/in LD with MDD only, 20 SNPs significantly linked to/in LD with T2D only, and 9 SNP significantly linked to/in LD with both T2D and MDD. The SNPs were statistically significant across different models. Two sets of LD blocks were MDD-specific, and one set was T2D-specific. *In silico* analysis of the risk variants predicted 3 variants with potential functional effects.
Conclusions: This is the first study to report *NR3C2* as a novel risk gene in T2D and MDD comorbidity. However, our results need to be replicated in other ethnicities.

1. Introduction

Impairments in the hypothalamic-pituitary-adrenal (HPA) axis and cortisol pathway and hypercortisolism may be major contributing factors to the common pathogenesis of major depressive disorder (MDD) and type 2 diabetes (T2D) (Bao and Swaab, 2019; Joseph and Golden, 2017). Stress exposure activating the HPA axis results in the release of corticosteroids which bind to two receptor types expressed in the brain and peripheral tissues: the glucocorticoid receptor (NR3C1) and the mineralocorticoid receptor (NR3C2) (Kino and Chrousos, 2004). The genes conferring HPA axis-related predisposition to the clinical association of T2D and MDD are the corticotropin-releasing hormone receptors (Amin et al., 2022a; Gragnoli, 2014), the melanocortin receptors (MC1R–MC5R) (Amin et al., 2022b), and possibly the glucocorticoid

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receptor (NR3C1) and the mineralocorticoid receptor (NR3C2) (Gragnoli, 2014). The mineralocorticoid receptor (NR3C2) binds aldosterone, which is a primary regulator blood pressure (Feldman, 2014). The mineralocorticoid receptor gene, named the nuclear receptor sub-family 3, group C, member 2 (NR3C2, also known as *MCR*) lies on chromosome 4 and is expressed in multiple tissues, including the central nervous system and the hippocampus (Uhlén et al., 2015).

NR3C2 appears to modulate stress and both basal and stress-induced cortisol axis activity, evaluation of stress appraisal, as well as memories associated to fear (ter Heegde et al., 2015). Increased expression and/or activity of brain mineralocorticoid receptors may avert as well as undo stress-related depression symptoms, whereas lower activities confer higher stress risk for depression (ter Heegde et al., 2015). Also, *NR3C2*-variants correlate with cognitive performance (Keller et al., 2017) and antidepressant response (Yuan et al., 2020) in depressed patients. Furthermore, a strong association between postpartum depression and the interaction of corticotropin-releasing hormone (CRH) with the *NR3C2* rs2070951 variant has been observed (Gutierrez-Zotes et al., 2020). On the other hand, higher expression of NR3C2 in the hippocampus and hypothalamus was associated in rodents with T2D (Jöhren et al., 2007) and in adipocytes with metabolic syndrome (Feraco et al., 2020; Urbanet et al., 2015). In humans, NR3C2 antagonists such as finerenone are approved treatments in heart failure and chronic kidney disease, significantly improving the outcomes in patients with T2D (Bakris et al., 2020; Filippatos et al., 2022), and variants in the *NR3C2* gene increase the risk of uncontrolled hypertension in patients with metabolic syndrome (Morales-Suárez-Varela et al., 2011). Previous studies of the *NR3C2* gene in MDD or T2D in humans were either inconclusive (i.e., no association was found (Lekman et al., 2014)) or the gene was implicated in a related phenotype, such as body mass index (BMI) (Fernandes-Rosa et al., 2010) or cognitive performance (Keller et al., 2017). To our knowledge, no study has so far reported risk variants in the *NR3C2* gene with either MDD and/or T2D. Given the *NR3C2* correlations with metabolic syndrome and antidepressant response, we hypothesized that the *NR3C2* gene might contribute to T2D, MDD, and MDD-T2D comorbidity. Thus, we aimed to explore whether its *NR3C2*-variants might be in linkage to or linkage disequilibrium (LD, namely, linkage and association) with familial T2D, MDD, and MDD-T2D comorbidity, studying families originating from the Italian peninsula.

2. Materials and Methods

We studied 212 multigenerational Italian families with an enriched family history of T2D and with MDD (DSM-IV diagnostic criteria) (Association., 2000). T2D was diagnosed by the presence of the classical signs and/or symptoms of diabetes plus elevated hyperglycemia, or by elevated fasting plasma glucose ≥140 mg/dl according the National Diabetes Data Group Criteria (Classification and diagnosis of diabetes, 1979). We then used the new American Diabetes Association criteria (at least two measurements of fasting glycemia at 126 mg/dl or higher, or random glycemia of at least 200 mg/dl or higher with symptoms, or at least 200 mg/dl or higher 2 h after an oral glucose tolerance test of 75 mg) after excluding secondary causes of diabetes (e.g. pancreatectomy). There were 1156 individuals in the 212 families analyzed (average family size, 5.45). In all, 590 were male (51%) and 566 were female (49%). A total of 115 individuals were diagnosed with MDD and 650 with T2D; T2D age of onset ranged from 7 to 81 years (mean 47.85; median 49).

We analyzed 86 microarray-single nucleotide polymorphisms (SNPs) within the *NR3C2* gene. The amplified variants passed quality control and genotyping, and Mendelian errors were excluded using PLINK (Purcell et al., 2007). The variants were then tested for parametric linkage to and/or linkage disequilibrium (LD) with T2D and/or MDD using Pseudomarker which is a powerful tool for detecting linkage and LD signals jointly or independently in a cohort of related or unrelated individuals (Hiekkalinna et al., 2011). We conducted the analysis of the variants for both linkage and LD across the model of dominance with complete penetrance (D1). We then performed a secondary analysis

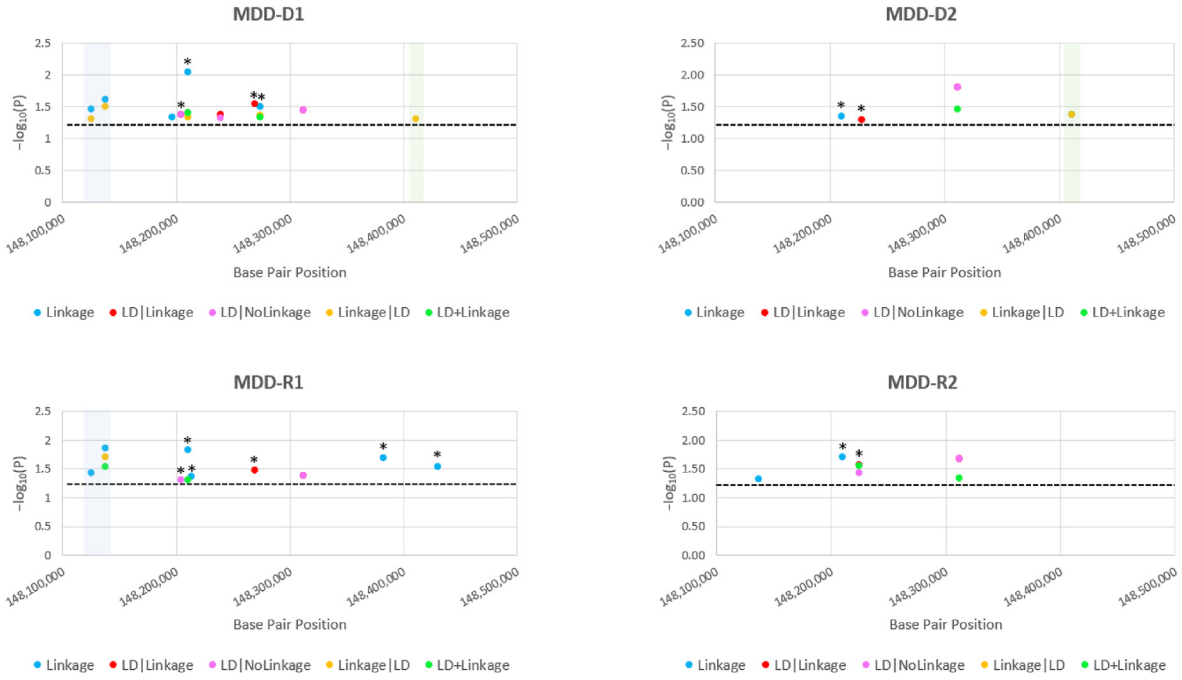

Fig. 1. Major Depressive Disorder (MDD) *NR3C2*-Risk Single Nucleotide Polymorphisms (SNPs).
For each *NR3C2*-risk single nucleotide polymorphisms (SNPs) in major depressive disorder (MDD), we present the −log10(P) as a function of each test statistic [(Linkage, linkage disequilibrium (LD)|Linkage, LD|NoLinkage, Linkage|LD, and LD + Linkage)] and per inheritance model. D1: dominant, complete penetrance, D2: dominant, incomplete penetrance, R1: recessive, complete penetrance, R2: recessive, incomplete penetrance. Colored rectangles mark the LD blocks (blue = Set01, green = Set02). Variants with an asterisk are comorbid MDD-T2D-risk variants. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

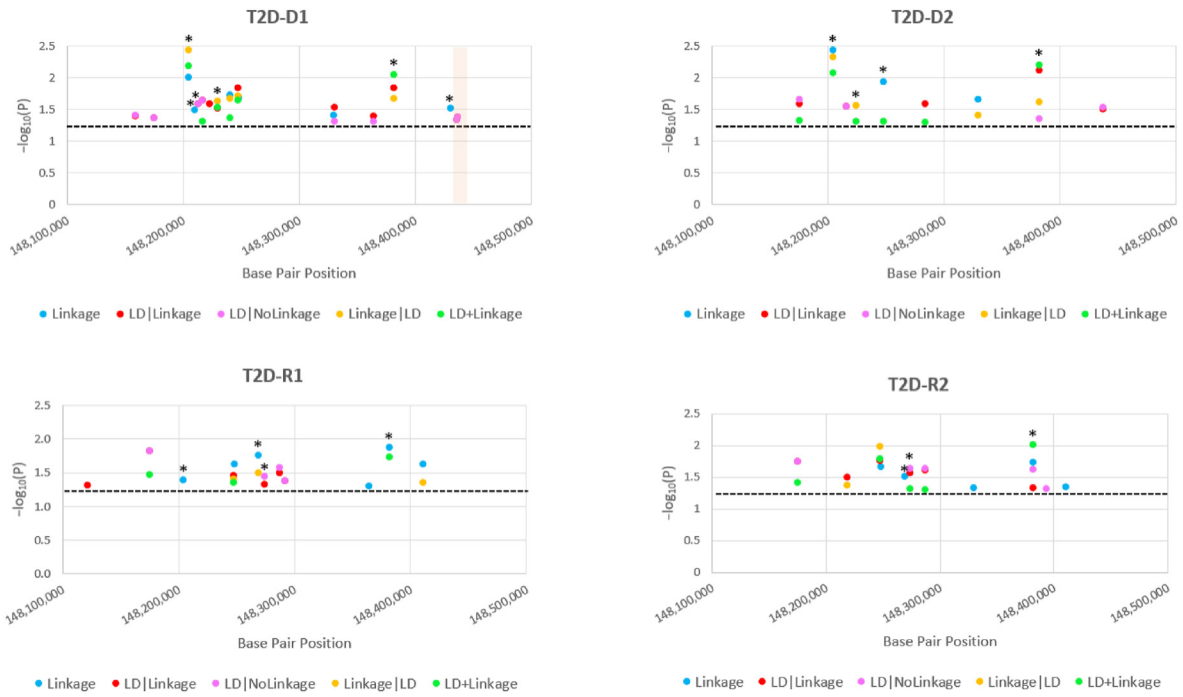

Fig. 2. Type 2 diabetes (T2D) NR3C2-Risk Single Nucleotide Polymorphisms (SNPs).
For each NR3C2-risk single nucleotide polymorphisms (SNPs) in type 2 diabetes (T2D), we present the −log10(P) as a function of each test statistic [(Linkage, linkage disequilibrium (LD)|Linkage, LD|NoLinkage, Linkage|LD, and LD + Linkage)] and per inheritance model. D1: dominant, complete penetrance, D2: dominant, incomplete penetrance, R1: recessive, complete penetrance, R2: recessive, incomplete penetrance. Light pink rectangle marks the LD block Set03. Variants with an asterisk are comorbid major depressive disorder (MDD)-T2D-risk variants. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

under the models dominant with incomplete penetrance (D2), recessive with complete penetrance (R1), and recessive with incomplete penetrance (R2). Data were fully deidentified. Bios Ethical Committee approved the study. P-values ≤ 0.05 were considered significant. To determine the presence of LD blocks (correlation of $r^2 \geq 0.9$), we calculated the r^2 of the risk SNPs using the LD matrix of the Tuscany Italian population derived from the 1000 Genomes Project (https://www.internationalgenome.org/data-portal/population/TSI). Variants that were not within an LD block were considered independent.

2.1. *In silico functional analysis*

We analyzed the MDD and T2D risk variants detected in our study with several functional and regulatory *in silico* prediction tools testing:

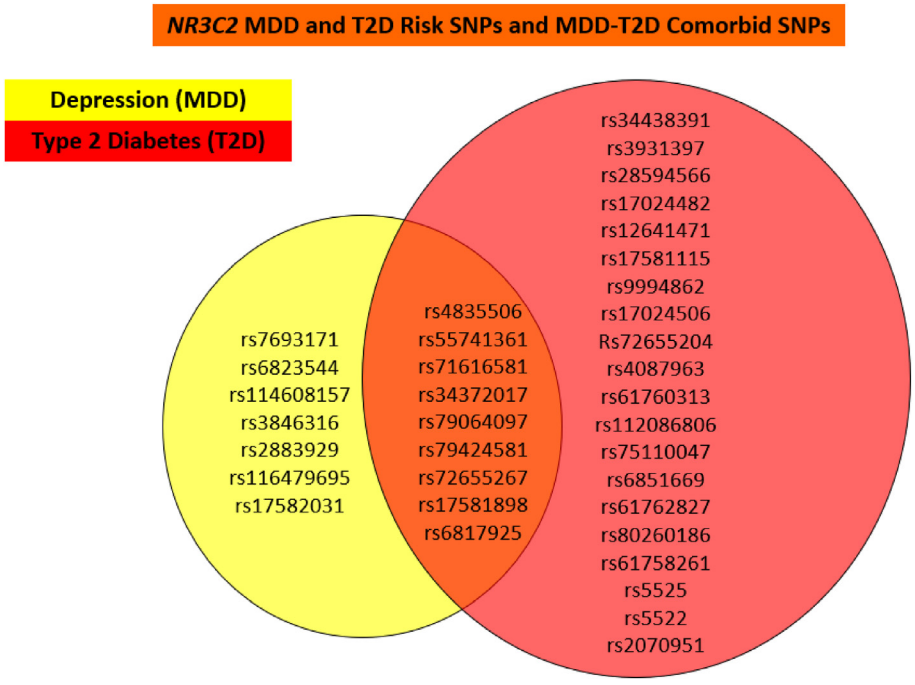

Fig. 3. *NR3C2* major depressive disorder (MDD) and type 2 diabetes (T2D) risk single nucleotide polymorphisms (SNPs) and MDD-T2D comorbid risk SNPs.

pathogenicity [SIFT (Ng and Henikoff, 2003), PolyPhen (Adzhubei et al., 2013)]; splicing [SpliceAI] (Jaganathan et al., 2019); transcription-factor binding [SNPnexus] (Dayem Ullah et al., 2018), SNP2TFBS (Kumar et al., 2017)]; and regulatory potential [RegulomeDB] (Boyle et al., 2012) and miRNA binding [mirSNP] (Liu et al., 2012).

3. Results

3.1. Linkage and linkage disequilibrium analysis

Our analysis revealed: 7 independent SNPs significantly linked to/in LD with MDD only (P-values $\leq$0.05) (Fig. 1); 20 SNPs significantly linked to/in LD with T2D only (Fig. 2); and 9 SNPs significantly linked to/in LD with both T2D and MDD (Figs. 1–3). The SNPs were statistically significant across different models (Table 1). Two sets of LD blocks were MDD-specific (Set01 with 2 risk variants and Set02 with 1 risk variant detected), and one set was T2D-specific (Set03 with 2 risk variants detected).

3.2. Results of in silico functional analysis

We found that the MDD-T2D rs4835506 comorbid variant affected the binding sites for transcription factor 3 (TCF3) and the MDD-T2D rs55741361 comorbid variant affected atonal bHLH transcription factor 1 (ATOH1). The T2D-risk rs9994862 variant was predicted to affect the binding of specificity protein 1 (SP1), which activates leptin transcription in response to insulin-mediated glucose metabolism (Moreno-Aliaga et al., 2007).

4. Discussion

The mineralocorticoid receptor is part of the essential HPA axis whose dysfunction could potentially contribute to the risk of MDD and/or T2D (Amin et al., 2022a, 2022b). The *NR3C2* gene is therefore a candidate gene for the T2D-MDD comorbidity. In this study, we report for the first time 36 novel risk variants in the *NR3C2* gene significantly linked to and associated with the risk of MDD, T2D, or T2D-MDD comorbidity. All

Table 1
Single nucleotide polymorphisms (SNPs) in the *NR3C2* gene found in our analysis to be significantly linked to major depressive disorder and type 2 diabetes.

Disease	Model[a]	SNP	Position	Ref	Alt	Risk Allele	Consequence	LD Block	Reported in MDD/T2D?
MDD	D1, R1	rs7693171	148124713	T	G	T	Intronic	Set01	Novel
	D1, R1, R2	rs6823544	148136828	G	A	G	Intronic	Set01	Novel
	D1	rs114608157	148196168	G	A	G	Intronic	Independent	Novel
	D1, R1	**rs4835506**	148208597	T	C	T	Intronic	Independent	Novel
	D1, D2, R1, R2	**rs55741361**	148209803	C	G	G	Intronic	Independent	Novel
	R1	**rs71616581**	148210120	G	A	G	Intronic	Independent	Novel
	R2	**rs34372017**	148224038	T	C	T	Intronic	Independent	Novel
	D2	**rs79064097**	148227442	T	C	C	Intronic	Independent	Novel
	D1	rs3846316	148238870	A	G	G	Intronic	Independent	Novel
	D1, R1	**rs79424581**	148268733	T	C	C	Intronic	Independent	Novel
	D1	**rs72655267**	148273197	G	A	A	Intronic	Independent	Novel
	D1	rs2883929	148299958	G	A	G	Intronic	Independent	Novel
	D1, D2, R1, R2	rs116479695	148311187	T	C	C	Intronic	NA	Novel
	R1	**rs17581898**	148381715	A	C	A	Intronic	Independent	Novel
	D1, D2	rs17582031	148410496	C	T	C	Intronic	Set02	Novel
T2D	R1	**rs6817925**	148430134	C	T	C	Intronic	Independent	Novel
	R1	rs34438391	148121370	A	G	A	Intronic	Independent	Novel
	D1	rs3931397	148158346	G	T	G	Intronic	Independent	Novel
	D1, D2, R1, R2	rs28594566	148174804	C	T	C	Intronic	Independent	Novel
	D1, D2, R1	**rs4835506**	148208597	T	C	T	Intronic	Independent	Novel
	D1	**rs55741361**	148209803	C	G	C	Intronic	Independent	Novel
	D1	**rs71616581**	148210120	G	A	A	Intronic	Independent	Novel
	D1, D2	rs17024482	148215583	A	G	G	Intronic	Independent	Novel
	R2	rs12641471	148218613	A	C	A	Intronic	Independent	Studied in MDD but not significant (Lekman et al., 2014)
	D1	rs17581115	148221334	A	G	G	Intronic	Independent	Novel
	D2	**rs34372017**	148224038	T	C	T	Intronic	Independent	Novel
	D1	**rs79064097**	148227442	T	C	C	Intronic	Independent	Novel
	D1	rs9994862	148239917	C	T	C	Intronic	Independent	Novel
	D1, R1, R2	rs17024506	148247158	T	C	T	Intronic	Independent	Novel
	D1, D2, R1, R2	rs72655204	148247777	G	A	A	Intronic	Independent	Novel
	R1, R2	**rs79424581**	148268733	T	C	T	Intronic	Independent	Novel
	R1, R2	**rs72655267**	148273197	G	A	G	Intronic	Independent	Novel
	D2	rs4087963	148283639	G	A	G	Intronic	Independent	Novel
	R1, R2	rs61760313	148286748	C	G	C	Intronic	Independent	Novel
	R1	rs112086806	148290660	T	C	T	Intronic	Independent	Novel
	D1, D2, R2	rs75110047	148329530	C	A	A	Intronic	Independent	Novel
	D1	rs6851669	148330657	T	C	C	Intronic	Independent	Novel
	D1, R1	rs61762827	148363890	G	A	A	Intronic	Independent	Novel
	D1, D2, R1, R2	**rs17581898**	148381715	A	C	C	Intronic	Independent	Novel
	R2	rs80260186	148393330	C	T	C	Intronic	Independent	Novel
	R1, R2	rs61758261	148410511	T	C	T	Intronic	Independent	Novel
	D1	**rs6817925**	148430134	C	T	C	Intronic	Independent	Novel
	D1	rs5525	148435364	A	G	A	Synonymous	Set03	Novel
	D1	rs5522	148436323	C	T	C	Missense	Set03	Symptoms of atypical depression (Hiekkalinna et al., 2011)
	D2	rs2070951	148436862	G	C	G	5′-UTR	Independent	Novel

[a] Models: D1: dominant complete-penetrance, D2: dominant incomplete-penetrance, R1: recessive complete-penetrance, R2: recessive incomplete-penetrance. The single nucleotide polymorphisms (SNPs) in bold are comorbid major depressive disorder (MDD)-type 2 diabetes (T2D) risk variants.

variants reported in our study are novel and have not been reported before in patients with either T2D or MDD.

Of note, the T2D-risk variant (rs12641471) was studied previously in MDD, and the association was statistically nonsignificant (Lekman et al., 2014). On the other hand, the T2D-risk variant rs5522 was part of a haplotype associated with low early-morning cortisol level and symptoms related to atypical depression (Kumsta et al., 2019). The same variant also mediated association between childhood emotional neglect and amygdala activity (Bogdan et al., 2012), and consistent with results in our study, the risk allele (C) was associated with higher BMI and LDL-levels (Fernandes-Rosa et al., 2010). The non-risk alleles of the T2D-risk variants rs5522 and rs2070951 in our study were previously reported in Asian patients with pseudohypoaldosteronism (Arai et al., 2003; Nam et al., 2017). This is highly relevant as pseudohypoaldosteronism is characterized by high blood levels of aldosterone due to resistance of NR3C2; the detected T2D-risk variants would, on the contrary, increase NR3C2 function and contribute to T2D and metabolic disease, which has been corroborated by findings in rodents (Jöhren et al., 2007; Feraco et al., 2020; Urbanet et al., 2015). The T2D-risk variant (rs2070951) was previously also found to interact with the *NR3C1*-variant rs1800445 in promoting aggressive behavior (Li et al., 2017). This highlights the pleiotropy of *NR3C2* variants and can explain their contribution to T2D and MDD risk.

The mechanism of *NR3C2* variants in contributing to T2D or MDD risk, as reported in our study, could potentially be explained by influencing the binding of transcription factors mediating neuronal and/or metabolic functions. In our study, *in silico* analysis predicted 3 variants (rs4835506, rs55741361 and rs9994862) with potential functional effects. The transcription factors' (ATOH1 and TCF3) bindings are influenced by two comorbid risk variants (rs55741361 and rs4835506). The T2D-MDD rs4835506 comorbid risk allele (T) alters the binding to TCF3, which binds to two short DNA sequences that regulate insulin secretion (Walker et al., 1990; UniProt, 1592), underlying a role in T2D. In addition, TCF3 is involved in neuronal differentiation (Long et al., 2020; Mulvaney and Dabdoub, 2012) which might underlie a co-pathogenic process in MDD and T2D (Dorsemans et al., 2017; Luna et al., 2021). These potential effects need to be tested *in vitro*. On the other hand, the MDD-risk allele (G) of the comorbid variant rs55741361 potentially binds to ATOH1, which is also involved in neuronal differentiation (Long et al., 2020; Mulvaney and Dabdoub, 2012), whereas the T2D-risk allele (C) disrupts the binding to ATOH1; thus, the effect of this variant might underlie different pathogenic processes for MDD and T2D. Since rs55741361 allele-G was both linked to and associated with MDD, while allele-C was only linked to T2D, the latter T2D variant, as well as the MDD variant, might indeed be in LD with other variant(s) expressing risk; or, their comorbidity risk might be played by different alleles of the same gene. Furthermore, the T2D-risk variant (rs9994862) altered the binding of specificity protein 1 (SP1), which activates leptin transcription in response to insulin-mediated glucose metabolism (Moreno-Aliaga et al., 2007). Of note, leptin is key in preventing metabolic disease: it has a central satiety effect on the hypothalamus and regulates body mass (Obradovic et al., 2021) as well as glucose metabolism both centrally and peripherally (Pereira et al., 2021). These predictions need to be tested *in vitro* to confirm their pathogenetic effect. The variants could be tested in *in vitro* skeletal muscle cell models (Sheng et al., 2022) in order to validate their roles in insulin sensitivity and glucose metabolism.

5. Conclusions

We identified 36 novel risk variants in the *NR3C2* gene significantly linked to and associated with the risk of MDD (16 variants), T2D (29 variants), or T2D-MDD comorbidity (9 variants). *In silico* analysis predicted potential functional impairments of 2 MDD-T2D comorbid variants (rs4835506, rs55741361) and of 1 T2D-risk variant (rs9994862). The results of our study could pave new ways for developing novel therapeutic modalities in T2D and MDD.

Authors' contributions

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

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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.

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Declaration of competing interest

The authors have declared that have no conflicts of interest.

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