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Linkage and association of novel DRD2 variants to the comorbidity of type 2 diabetes and depression

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Abstract. – OBJECTIVE: The dopamine receptor 2 (*DRD2*) binds dopamine in both central tissues (e.g., basal ganglia, pituitary gland) and peripheral tissues (e.g., adrenal gland, kidneys, intestine) and mediates dopamine actions in cognition, emotional processing, and prolactin-secretion inhibition and stimulation, and in *DRD2-/-* knockout mice insulin secretion is impaired. Variants in or around the *DRD2* gene have been implicated in major depressive disorder (MDD), schizophrenia, obesity, and type 2 diabetes (T2D) but not in comorbid MDD-T2D patients; *DRD2* agonists (e.g., bromocriptine) are approved treatments in T2D. This study aimed to detect whether the *DRD2* gene plays a role in T2D, MDD, and T2D-MDD comorbidity in Italian families.

SUBJECTS AND METHODS: In 212 Italian families with T2D and MDD, we investigated the presence of linkage and linkage disequilibrium of variants in the *DRD2* gene with T2D and/or MDD. A test was considered statistically significant if p was <0.05.

RESULTS: We found 3 novel variants (rs6276, rs35608204, and rs1800499) significantly linked to and/or associated with the risk of T2D and 1 novel variant (rs112646785) significantly linked and associated to the comorbidity of T2D and MDD.

CONCLUSIONS: This is the first study to link and associate *DRD2* variants with the comorbidity of T2D and MDD.

Key Words:
Dopamine receptor 2, *DRD2* gene, Dopamine, Prolactin, PRL, Major depressive disorder, Depression, MDD, Psychiatric disorder, Type 2 diabetes, T2D, Metabolic, Comorbidity, Mental-metabolic, Linkage disequilibrium, LD block, Single nucleotide polymorphism, SNP, Schizophrenia, SCZ, Insulin secretion, Glucose intolerance, Obesity, Cognition, Emotional processing, *DRD2-/-*, Knockout mice, Basal ganglia, Pituitary gland, Peripheral tissues, Adrenal gland, Kidneys, Intestine, Locomotion, Energy homoeostasis, Antipsychotic medications, β-cells, Agonists, History, Diagnostic criteria, DSM-IV, Mendelian error, PLINK, Pseudomarker, Parametric, Dominant, Recessive, Complete penetrance, Incomplete penetrance, Inheritance model, Statistically significant, Risk allele, RegulomeDB, rs6276, rs35608204, rs1800499, rs112646785, Chromatin state, Endocrine pancreas, Hyperglycemia, Anxiety, Migraine.

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Introduction

Dopamine is an important neurotransmitter that exerts a multitude of physiologic functions, including emotional processing, locomotion, cognition, and behavior and energy homoeostasis[1-3]. The dopamine system has long been studied in relation to susceptibility and treatment of psychiatric disorders [e.g., schizophrenia (SCZ), depression][4], and it has also been studied in relation to metabolic disorders [e.g., obesity, type 2 diabetes (T2D)][5,6]. The roles of dopamine are mediated by five dopamine receptors (DRD1-DRD5)[7]. The dopamine receptor 2 (*DRD2*) is the main target for antipsychotic medications[8]. *DRD2* binds dopamine in both central tissues (e.g., basal ganglia, pituitary gland) and peripheral tissues (e.g., adrenal gland, kidneys, intestine), mediates its actions in cognition[9], emotional processing[10], and prolactin-secretion inhibition and stimulation[11], and impairs insulin secretion in *DRD2*-/- knockout mice[12]. Recent evidence shows that modulating the activity of *DRD2* affects pancreatic insulin production in mice and cultured β-cells[13,14]. *DRD2* agonists (e.g., bromocriptine) are approved treatments in T2D[15]. Variants in or around the *DRD2* gene which encodes *DRD2* have been implicated in major depressive disorder (MDD)[16], SCZ[17], obesity[18], and T2D[19] but not in comorbid MDD-T2D patients. In this study, we aimed at investigating the role of *DRD2* variants in the susceptibility to familial T2D and MDD comorbidity.

Subjects and Methods

We accessed the deidentified data of 212 Italian families with T2D, rich T2D familial history, phenotyped for the presence or absence of MDD (diagnostic criteria of DSM-IV). Participants were recruited from central Italy following the Helsinki Declaration guidelines and provided written informed consent. The study was institutionally approved by the Bios Ethical Committee.

Statistical Analysis

We amplified 21 microarray-based single nucleotide polymorphisms (SNPs) in the *DRD2* gene and excluded genotyping and Mendelian error *via* PLINK[1]. Using Pseudomarker[20], we analyzed the 21 SNPs for 2-point parametric-linkage to and linkage-disequilibrium (LD) with T2D with the recessive complete penetrance (R1) model. Subsequently, we tested the variants for the dominant complete penetrance (D1), dominant incomplete penetrance (D2), and recessive incomplete penetrance (R2) models. The T2D-risk variants were tested for linkage to and LD with MDD under the same models. Only tests with $p < 0.05$ were considered statistically significant. The risk SNPs were labelled "independent" if they were not found in a specific LD block in the Tuscany Italian population (https://www.internationalgenome.org/data-portal/population/TSI).

Results

We found a total of 3 variants (rs6276, rs35608204, and rs1800499) significantly linked to and/or associated with T2D and 1 variant (rs112646785) significantly linked and associated to the comorbidity of T2D and MDD (Table I). Linkage and LD (i.e., linkage and association) were statistically significant across different inheritance models (Figure 1).

Discussion

The 3 T2D-risk variants and the MDD-risk variant identified in the present study are novel and have not been previously reported with T2D, MDD, or T2D-MDD comorbidity. The two T2D-risk variants (rs6276 and rs1800499) were studied with SCZ[21,22] and the non-risk allele C of rs6276 (but not rs1800499) was significantly associated with SCZ-risk[22]. Regulatory predictions for the SNPs in our study using RegulomeDB[23] revealed that all T2D and MDD risk variants detected in our study intersect with repressed chromatin state in the endocrine pancreas, which is consistent with impaired insulin secretion and glucose intolerance reported in *DRD2*-/- knockout mice[12].

Interestingly, variants in the *DRD2* gene were previously associated with the comorbidity of hyperglycemia and SCZ[24], and the comorbidity of MDD and anxiety and migraine[25].

Table I. Risk Single Nucleotide Polymorphisms (SNPs) in the *DRD2* Gene Linked to and/or in Linkage Disequilibrium (LD) with Major Depressive Disorder (MDD) and/or Type 2 Diabetes (T2D).

Disease	Model[1]	SNP	Position	Ref	Alt	Risk Allele	Consequence	LD Block	Reported in MDD or T2D?
MDD	D2, R1, R2	**rs112646785**	113444554	T	C	T	Intronic	Independent	Novel
T2D	D2	rs6276	113410675	C	T	T	3'UTR	NA	Novel
	D1, D2	rs35608204	113415071	A	G	G	Intronic	Independent	Novel
	D1, D2, R1, R2	rs1800499	113416972	C	T	T	Synonymous	Independent	Novel
	D1, R1, R2	**rs112646785**	113444554	T	C	T	Intronic	Independent	Novel

[1]Models: D1: dominant, complete penetrance, D2: dominant, incomplete penetrance, R1: recessive, complete penetrance, R2: recessive, incomplete penetrance. The MDD-T2D comorbid risk variant is bolded.

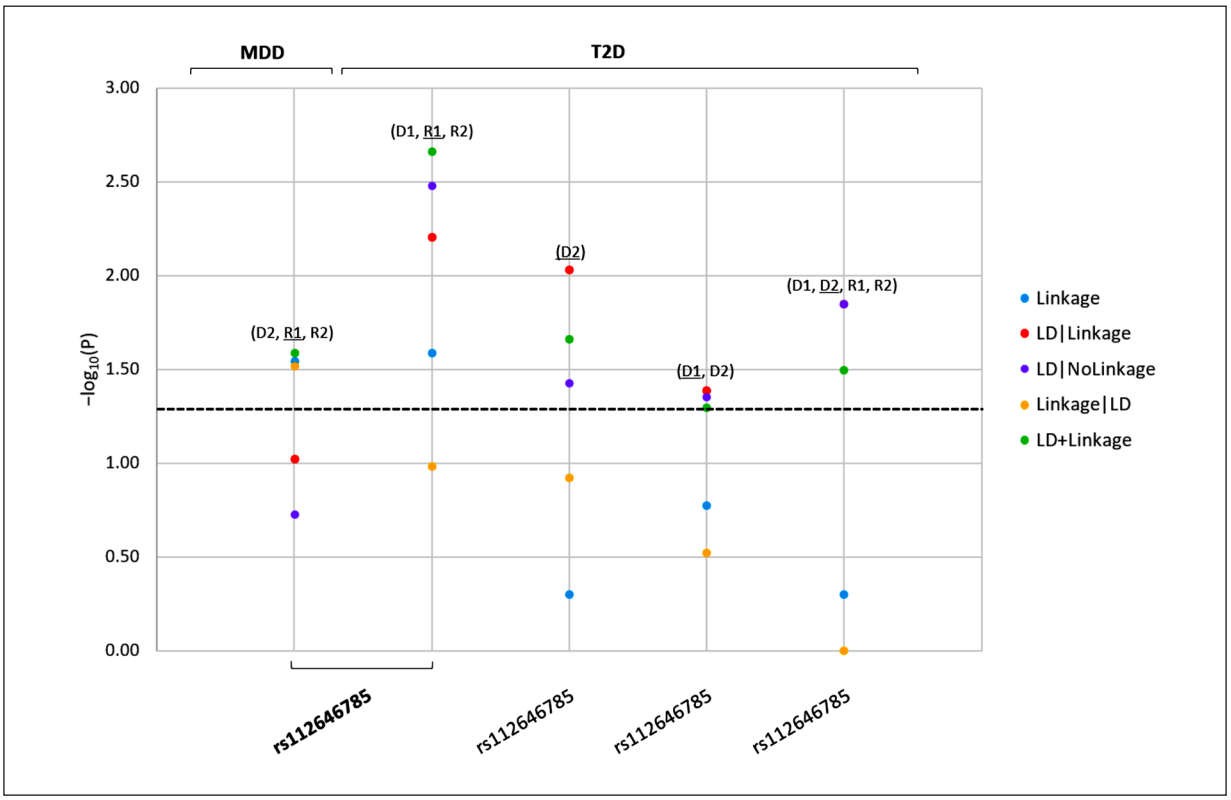

Figure 1. Major Depressive Disorder (MDD) and Type 2 Diabetes (T2D) *DRD2* Risk Single Nucleotide Polymorphisms (SNPs) Linkage and Linkage Disequilibrium (LD) Analysis Results. For each significant risk single nucleotide polymorphism (SNP) in the *DRD2* gene, we present the −log10(*p*) as a function of each test statistic (Linkage, LD|Linkage, LD|NoLinkage, Linkage|LD, and LD+Linkage) and label the inheritance model: D1: dominant, complete penetrance, D2: dominant, incomplete penetrance, R1: recessive, complete penetrance, R2: recessive, incomplete penetrance. For each SNP we present the most significant test statistics between the significant models (model underlined). The bolded SNP is comorbid for major depressive disorder and type 2 diabetes.

Conclusions

Our study is the first linking and associating *DRD2* variants with the comorbidity of T2D and MDD. Peninsular families are powerful and genetically informative as they allow the reveal of gene variants contributing to complex disorders, such as T2D and MDD as well as to their comorbidity.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Ethics Approval

Subjects provided written informed consent and were recruited following the Helsinki declaration guidelines. Bios Ethical Committee approved the study.

Informed Consent

Written informed consent was obtained by participants before the study.

Authors' Contribution

Claudia Gragnoli conceived and supervised the project, including statistical analysis and manuscript drafting. M.

Amin helped with the bioinformatic analysis, literature search, and manuscript drafting. R.-L. Wu and T.T. Postolache critically helped in data interpretation and critical revision of the manuscript. All authors have approved the final manuscript.

Data Availability

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

Authors' Information

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