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RAPID COMMUNICATION

# The role of melatonin receptor 1B gene (*MTNR1B*) in the susceptibility to depression and type 2 diabetes comorbidity

Melatonin is an endogenous monoamine hormone secreted by the pineal gland. Melatonergic signaling has been shown to play a role in circadian rhythm regulation, lipid and glucose metabolism, and obesity, and it has anti-inflammatory and antioxidant properties. The melatonin receptor 1B gene (*MTNR1B*) is expressed in, among other tissues, the brain and pancreatic beta cells, and risk variants for T2D have been reported as impairing early insulin secretion and increasing fasting glucose levels.[1] Variants in the *MTNR1B* gene also have been reported in patients with depression (MDD).[2]

*MTNR1B* variants have therefore been reported to be one of the genetic risk factors for T2D and MDD, albeit independently of each other thus far. The genetic basis for the strong comorbidity between T2D and MDD remains to be fully elucidated. In this study, we aimed to evaluate in Italian families whether *MTNR1B* variants are in linkage to and/or linkage disequilibrium (LD, *i.e.*, association) with familial MDD, T2D, and/or MDD-T2D comorbidity.

We accessed the fully deidentified data of 212 families, descended from at least three Italian generations with T2D and family history of T2D. For T2D diagnosis, we used the National Diabetes Data Group Criteria, for which T2D can be diagnosed by the presence of the classical signs and/or symptoms of diabetes with unequivocally elevated hyperglycemia, or by fasting plasma glucose $\geq$140 mg/dL. Upon subsequentially updating the T2D status of initially unaffected subjects, we used the new American Diabetes Association criteria with the cut-off of 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. Secondary causes of diabetes were excluded (*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). The families were also phenotyped for MDD according to DSM-IV.

Using these data, we tested seven microarray-derived SNPs in the *MTNR1B* gene. We excluded genotyping and Mendelian errors via PLINK. We analyzed the SNPs for 2-point parametric linkage and linkage disequilibrium (LD) (*i.e.*, linkage + association) to/with T2D and MDD. We used the following Pseudomarker test statistics: Linkage, LD|Linkage, LD|NoLinkage, Linkage|LD, and LD + Linkage, and considered that variants with at least three tests with $P < 0.05$ would confer risk. We used four models: dominant and complete penetrance (D1), dominant and incomplete penetrance (D2), recessive and complete penetrance (R1), and recessive and incomplete penetrance (R2) (Pseudomarker). To compute LD blocks within the risk variants, we used the Tuscany Italian population from the 1000 Genomes Project (https://www.internationalgenome.org/data-portal/population/TSI) and considered SNPs significantly correlated ($r^2 \geq 0.9$) to be within the same LD block; otherwise, SNPs were labeled as independent. The Bios Ethical Committee approved the study.

We identified two missense (rs8192552 G> A, putative risk allele G and rs61747139 A > G, putative risk allele G) and two intronic variants (rs10830963C > G, putative risk allele C and rs11020131 G> A, putative risk allele G) significantly linked to and/or associated with the risk for T2D; one missense variant (rs8192553 G> A, putative risk allele A) significantly linked to and/or associated with the risk for MDD; and one intronic variant (rs4601728 A > G) significantly linked to and/or associated with both the risk for T2D (putative risk allele A) and MDD (putative risk allele G). All variants were independent. The results of the Pseudomarker analyses of the

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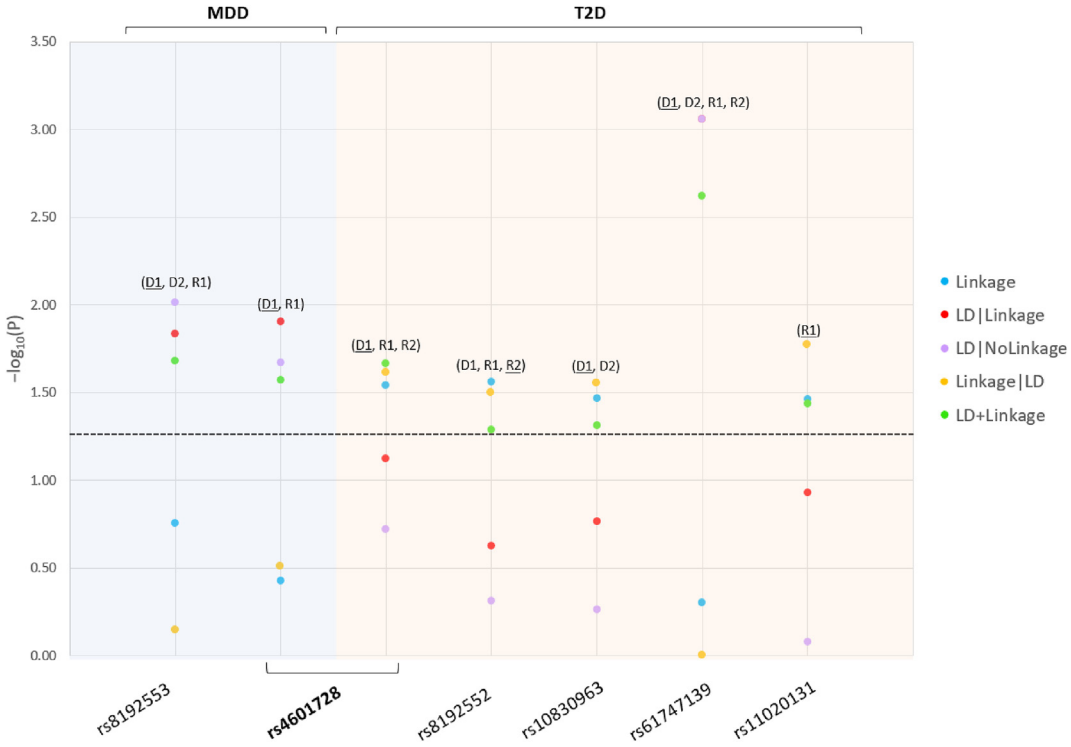


**Figure 1** Linkage and linkage disequilibrium analyses results of major depressive disorder (MDD) and type 2 diabetes (T2D) risk variants. For each *MTNR1B*-risk single nucleotide polymorphism (SNP) in T2D and MDD, we present the −log10(P) as a function of each test statistic (Linkage, Linkage Disequilibrium (LD)|Linkage, LD|NoLinkage, Linkage|LD, and LD + Linkage) and per the significant inheritance models: D1: dominant, complete penetrance; D2: dominant, incomplete penetrance; R1: recessive, complete penetrance; R2: recessive, incomplete penetrance. For each SNP, we underline the most significant test statistic across the significant models. The bolded SNP is comorbid for MDD and T2D.

significant parametric models for MDD and T2D are reported in Figure 1.

This study reported novel *MTNR1B* variants linked to and/or associated with the risk of isolated or combined T2D and MDD. The MDD-risk variant (rs8192553) and the two T2D-risk variants reported in our study (rs61747139 and rs8192552) have been studied before in T2D, but no significant association has been reported. The T2D non-risk allele (A) of the SNP rs8192552, however, was previously found to be significantly associated with impaired glucose fasting,[3] insulin resistance in obese patients, and waist circumference. On the other hand, the non-risk allele (G) of the T2D-risk SNP rs10830963 was found to be significantly associated with the risk of T2D in the Czech population.[4] The discrepancy of these results might be explained by the presence of an underlying pathogenetic variant in LD with rs8192552 or in LD with rs10830963. Furthermore, the same T2D-risk SNP rs10830963 was previously investigated as a risk for T2D-MDD comorbidity, and although significant associations were found with T2D and MDD individually, no significant association with comorbidity was found.[5] The rs4601728 SNP might be a marker for the linkage between T2D and MDD, but given the risk allelic difference found, it might be in LD with other markers contributing to the phenotypes. This is therefore the first report on *MTNR1B* variants linked to T2D-MDD coexistence, a highly prevalent and salient comorbidity with considerable morbidity and early mortality implications.

## Author contributions

C.G. conceived and supervised the project, including statistical analysis and manuscript drafting. B.R. helped with 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 approved the final manuscript.

## Conflict of interests

The authors have declared that have no conflict of interests.

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## Data availability

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

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