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LETTER

The prolactin receptor (*PRLR*) gene is linked to and associated with the comorbidity of depression and type 2 diabetes in Italian families

Major depressive disorder (MDD) and type 2 diabetes (T2D) are two common complex multifactorial disorders that share several genetic and environmental risk factors such as hypercortisolism and related genes' risk variants within the stress response and the neuroendocrine hypothalamic-pituitary axis. Under stress, the pituitary gland releases prolactin (PRL), whose effects are pleiotropic and include mood control and insulin secretion from the beta cells.[1] Variations in the prolactin receptor (*PRLR*) gene are associated in rodent models with stress level, depression-like behavior,[2] and hepatic insulin sensitivity[3] and in humans with maternal glucose homeostasis and gestational diabetes.[4] Furthermore, prolonged breastfeeding has been associated with reduced incidence of T2D, potentially related to PRL action. To our knowledge, no studies are reporting *PRLR* as a risk gene for MDD or T2D. Therefore, we aimed to investigate if the *PRLR* gene encoding for the PRLR plays a role in the familial comorbidity of MDD and T2D.

In 212 Italian families phenotyped for T2D and MDD, we investigated 41 microarray-based single nucleotide polymorphisms (SNPs) in the *PRLR* gene. We tested the variants for linkage/linkage-disequilibrium (LD, *i.e.*, association) to/with T2D and MDD using recessive and dominant models with incomplete penetrance. To test whether the risk variants were linked/in LD under complete penetrance a s well, we ran a secondary parametric analysis. We performed genotyping and Mendelian error exclusion using PLINK. A *P*-value < 0.05 was used as the cut-off for the level of statistical significance. The study was approved by the Bios Ethical Committee.

We found a total of 13 risk variants significantly linked/in LD to/with T2D and/or MDD ($P < 0.05$) (Table S1). Three risk variants (rs79880058, rs4703396, and rs1604428) were significantly linked/in LD to/with MDD (Fig. S2); four risk variants (rs114771776, rs113983456, rs6878981, and rs37386) were significantly linked/in LD to/with T2D (Fig. 1); and six risk variants (rs80180294, rs2228482, rs12655058, rs6897987, rs75392528, and rs4425481) were significantly linked/in LD to/with both MDD and T2D, three of which have concordant risk alleles. The T2D-risk rs114771776 and rs113983456 were within a specific LD block, and the T2D-risk rs6878981 and MDD-T2D-risk rs2228482 were in another specific LD block. Significant variants within a specific LD block replicate each other and perpetuate the pleiotropic effect of the *PRLR* gene in mediating MDD-T2D co-morbidity. All these risk variants are novel and were not previously reported in MDD, T2D, or another related phenotype. *In silico* analysis predicted that the comorbid MDD-T2D rs6897987 risk SNP has a high regulatory potential (RegulomeDB score 1 [0—1]) and is located at a peak of chromatin immunoprecipitation (Chip-seq) site, suggesting that it is a binding site for transcription factors without, however, a known transcription factor predicted to bind to it. This is the first study to link the *PRLR* gene to the risk of morbidity and comorbidity of MDD and T2D. The *PRLR* gene may play a mental-metabolic role, possibly through activation of the Janus Kinase/Signal Transducers and Activators of Transcription pathway which is involved in stress response and metabolic homeostasis.[5] Functional studies are needed to confirm these results.

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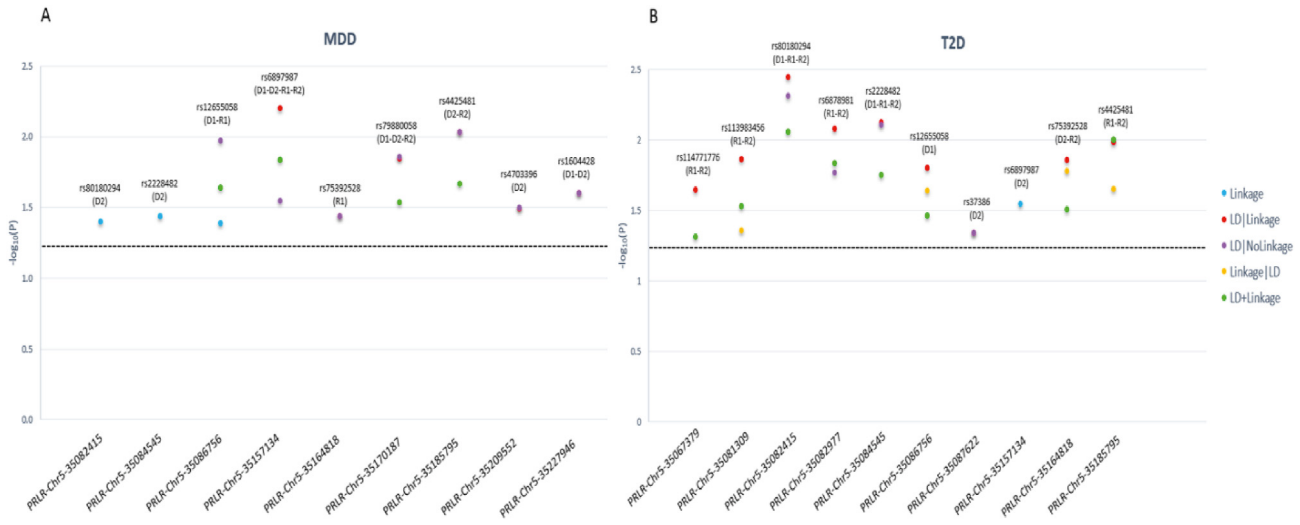

Figure 1 MDD and T2D PRLR risk SNPs linkage and LD analysis results. For each significant major depressive disorder **(A)** and type 2 diabetes **(B)**-risk SNP in the *PRLR* gene, we present the −log10(P) as a function of each significant test statistic (Linkage, LD|Linkage, LD|NoLinkage, Linkage|LD, and LD + Linkage) across the significant inheritance model(s): D1: dominant, complete penetrance; D2: dominant, incomplete penetrance; R1: recessive, complete penetrance; R2: recessive, incomplete penetrance.

Ethics declaration

Families were recruited following the Helsinki Declaration guidelines. The Bios Ethical Committee approved this study. Individuals provided written informed consent before participation.

Author contributions

C.G. conceived and supervised the project, including statistical analysis and manuscript drafting. 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 they 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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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gendis.2023.06.018.

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