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CRHR1 gene shows extensive linkage to major depression and type 2 diabetes in Italian families

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Background: Major Depressive Disorder (MDD) and Type 2 Diabetes (T2D) are heterogeneous polygenic and complex disorders and are often comorbid. This shared comorbidity can be partially explained by several genetic, environmental, and hormonal factors such as hypercortisolism in MDD and a subset of patients with T2D. CRH receptor-1 (CRHR1) dysfunction may explain the MDD- and T2D-hypercortisolism, at least in a subgroup of patients. CRHR1-variants predisposing to impaired CRHR1 dosage and/or function may lead to hypercortisolism (substrate for serotonin dysfunction and MDD), as well as hyperglycemia, insulin resistance, and increased visceral fat, all T2D-traits. We hypothesize that CRHR1-variants may impair the stress and cortisol response, conferringincreased risk for MDD, T2D, and MDD-T2D comorbidity. **Methods:** Using 212 Italian families with T2D, enriched T2D-familial history, and MDD, we amplified and tested 158 CRHR1 SNPs by two-point parametric analysis for linkage and linkage-disequilibrium (LD), using the models dominant (D) and recessive (R), with complete (1) and incomplete (2) penetrance (Pseudomarker). **Results:** We detected linkage to and/or LD with MDD: for 93 SNPs (D1), 57 SNPs (D2), 91 SNPs (R1), and 14 (R2); and T2D for 15 SNPs (D1), 18 SNPs (D2), twelve SNPs (R1) and ten SNPs (R2), for a total of 122 SNPs. Specific LD-blocks' underlined each disorder without overlap. Of note, three independent SNPs were comorbid forMDD and T2D. All risk SNPs are intronic, except for one synonymous, one splice site, one missense, and one 3'UTR. In-silicoanalysis detected functional gene and tridimensional protein changes in a risk-SNP. **Conclusion:** We are the first to report CRHR1 in linkage and LD with MDD and T2D in T2D-families. CRHR1contribution to MDD appears stronger thanthe contribution to T2D and may thus antecede its onset . Genetically impaired stress and cortisol response may lead to comorbid MDD-T2D, likely a molecular-clinical entity in a subset of families. Our findings should be replicated in families from other ethnic groups.

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